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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insur... Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1948

ORIGINAL ARTICLES

CHRONIC CONSTRICTIVE PERICARDITIS
A STUDY OF 53 CASES

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(From the Massachusetts General Hospital)

SINCE 1914, 53 cases of chronic constrictive pericarditis have been seen at the Massachusetts General Hospital and in the private practice of one of us (P.D.W.). Some of these cases have been described in previous publications.[3,7] With the addition of new case material, it seemed wise to review our experience, both to analyze more closely the clinical picture and to evaluate the long-term results of surgery. In addition we have summarized for the first time the pathological findings on those patients who succumbed to the disease or to its complications and on whom autopsy data are available.

The patient who complains of shortness of breath, increase in girth, and swelling of the ankles, who shows prominence of the neck veins, hepatomegaly, and peripheral edema, and yet has a quiet and often normal-sized heart may offer a puzzling diagnostic problem. A high index of suspicion is needed in these patients with unexplained heart failure or with atypical cirrhosis of the liver, if the diagnosis of constrictive pericarditis is to be made. The absence of clearcut evidence of other types of heart disease, the helpful Roentgen-ray pictures, and the more or less characteristic electrocardiographic pattern are the most valuable clues. As we have become familiar with the effects of cardiac constriction it has been easier to detect these cases. Despite the most careful studies, however, the etiology still remains obscure in many instances, the diagnosis sometimes difficult, and the treatment far from a simple matter. It should be emphasized that except in very mild cases the disease is a serious

one, carrying with it a considerable disability and mortality, notwithstanding the encouraging advances in surgical treatment.

1. **Clinical Data Concerning Our 53 Cases.** A. *Sex.* There were 36 males (67.9%) and 17 females (32.1%) in the series.

B. *Age of onset of symptoms of chronic constrictive pericarditis.* The number of cases for each age group is indicated in Table 1.* Our youngest patient became ill at the age of 16 months and our oldest at the age of 58 years. Over 70% of the group were between the ages of 10 and 40 years.

TABLE 1.

AGE AT ONSET OF SYMPTOMS OF CHRONIC CONSTRICTIVE PERICARDITIS
(52 Cases)

Age in Years	Number of Cases	% of Total
0–9 years	1	1.9
10–19 years	13	25.0
20–29 years	13	25.0
30–39 years	11	21.1
40–49 years	7	13.5
50–59 years	7	13.5

TABLE 2.

DURATION OF SYMPTOMS OF CHRONIC CONSTRICTIVE PERICARDITIS
(prior to first visit to us)

Years	Number of Cases	% of Total
0 (no symptoms)	1	1.9
0–1	18	33.9
2–4	19	35.8
5–9	10	18.9
10–19	3	5.7
20–29	2	3.8

C. *Duration of symptoms of chronic constrictive pericarditis prior to first visit to us.* (These figures are to be found in Table 2.) 65% of the patients had noted symptoms for 2 years or more. The longest total duration of symptoms has been 44 years.

D. *Initial symptoms.* It is of interest to ascertain what symptoms were first troublesome. In some cases, 2 or even 3 symptoms appeared together at the onset. (These are indicated in Chart 1.) Dyspnea on effort was by far the most common initial complaint, being followed in order by swelling of the ankles and shins, abdominal swelling, palpitation, and weakness. The lack of breathlessness in cases of constrictive pericarditis has sometimes been a matter of comment, but it is obvious from this analysis that the patients themselves were aware of a definite diminution in their exercise tolerance. Orthopnea as an initial symptom was found, however, only three times.

E. *Symptoms when first seen by us.* (Chart 1 also lists all symptoms which were mentioned by the patients when interrogated on their first visit to us.) It will be seen that these are very similar in their incidence to those causing complaint at the onset of the disease, although orthopnea is found with increasing frequency. Again, shortness of breath on effort was the outstanding complaint. Investigation of the group of patients who were

* We have not included in Table 1 one patient, aged 23 years, who was symptom-free despite clear evidence of pericardial constriction.

dyspneic (41 cases) as contrasted with the smaller group of patients who were not (12 cases) shows an almost identical incidence of unilateral and bilateral pleural effusions (as found by Roentgen-ray), ascites, and auricular fibrillation or flutter. It would therefore appear that shortness of breath is not necessarily the result of a reduction in the lung volume secondary to hydrothorax or a high diaphragm, or to the presence of a cardiac arrhythmia, but is consequent to a reduced pulmonary blood flow, or to congestion in the pulmonary circulation, resulting from cardiac tamponade.

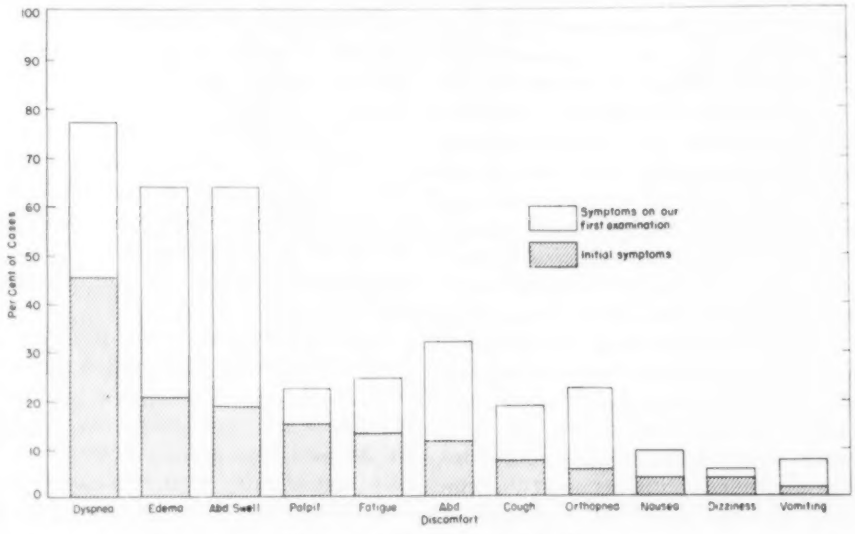

Chart 1. Symptoms (53 Cases)

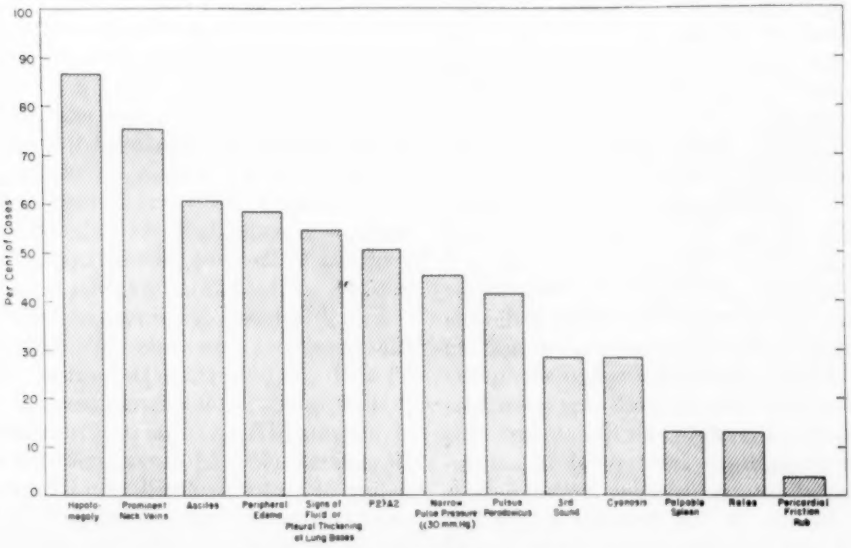

Chart 2. Physical Findings (53 Cases)

F. *Physical findings when first examined.* An enlarged liver was the commonest finding, and the actual incidence of hepatomegaly is undoubtedly higher than is indicated on Chart 2, due to the fact that liver enlargement could not be demonstrated where marked ascites was present. Prominence or pulsation of the cervical veins (with the patient in the erect position) was noted in 75% of the patients but was probably present, in minor degree at least, in the remainder. Ascites, peripheral edema, and signs of pleural fluid or pleural thickening were found in the majority. The fact that approximately half of the patients were observed to have an accentuation of the second sound in the pulmonic area is a significant physical finding, both in view of the incidence of dyspnea and the relatively few (22%) who were under 20 years of age when examined. It suggests the importance of left, as well as right, ventricular constriction. Another interesting auscultatory finding was the presence of a distinct third sound at the apex or at the lower left sternal border, or at both areas, in 15 of the cases. Slightly less than half of the group showed narrowing of the pulse pressure (and this was marked in only 4 patients) or pulsus paradoxicus. Uncommon were râles in the lung fields, splenomegaly, and a pericardial friction rub.

No consequential murmurs were noted, except in 3 patients. A loud apical systolic murmur was heard in 2 patients, 1 of whom showed aortic stenosis at autopsy. In a third patient a loud systolic murmur was found in the fourth intercostal space along the left sternal border and was accompanied by a systolic thrill; at first this was thought to be typical of an incidental interventricular septal defect, but of late it has become much less loud and is now considered to be of doubtful significance.

G. *Heart size.* Determination of the heart size by physical examination was unreliable, due to the frequency of pleural thickening and effusion and because of the feeble character of the apex impulse. Roentgenographic observations were made on admission in each case, however, and revealed a normal cardiac shadow in 24 patients (45.2%), a slight increase in size in 9 (17.0%), a moderate enlargement in 17 (32.1%), and a greatly enlarged heart in only 3 (5.7%).

H. *Incidence of calcification in the pericardium.* Calcium was demonstrated to be present in the pericardium by Roentgen-ray study, observations at the time of operation, or postmortem examination in 29 of the 53 cases (54.7%).

I. *Cardiac pulsations as observed by fluoroscopy.* No information is available on the character of the pulsations of the heart in 13 patients (24.5%). In 26 patients (49.0%) fluoroscopy at the time of admission revealed a definite diminution of the pulsations of the heart, at times limited to one border, and in 6 patients (11.3%) there were no cardiac pulsations visible. It is very important to note that in 8 cases (15.2%) normal excursions of the heart were described.

J. *Incidence of hydrothorax.* Chest Roentgen-ray films disclosed that pleural fluid was present in 28 of the 53 cases (52.8%). This was limited to the right pleural cavity in 11 patients, was confined to the left pleural cavity in 3 patients, and was bilateral in 14.

K. *Electrocardiographic findings.* Electrocardiograms were available on 52 of the 53 patients in the series. The rhythm was normal throughout in 32 of these (61.5%). In the remaining 20 patients (38.5%) abnormalities consisting of auricular fibrillation (18 cases) or of auricular flutter (5 cases, in 3 of which auricular fibrillation was also noted) were present as follows:

auricular fibrillation, apparently permanent (6 of these cases were operated upon)..... 12 cases
auricular fibrillation with one transient reversion to normal rhythm (no operation performed) ..... 1 case
normal rhythm followed by apparently permanent auricular fibrillation (no operation performed) ..... 2 cases
normal rhythm followed postoperatively by auricular flutter, then fibrillation, apparently permanent ..... 1 case
auricular flutter followed postoperatively by auricular fibrillation, apparently permanent. 2 cases
auricular flutter, apparently permanent (surgery performed).. 1 case
auricular flutter, transient, postoperative only..... 1 case

It will be observed that in no instance was partial resection of the pericardium followed by normal rhythm when an arrhythmia existed prior to operation. It is also of interest that the 32 patients whose rhythm was normal at the time of admission had been having symptoms for an average period of only 2.8 years, whereas the 15 patients whose rhythm was abnormal on admission and remained so had an average duration of symptoms of 7.4 years. The rhythm was described as clinically normal in the one patient who had no electrocardiogram recorded.

The height of the greatest QRS complex in the limb leads was no greater than 3 mm. in 17 cases (32.6%); left axis deviation was found twice and right axis deviation only once. The T waves in all the limb leads were low, flat, or inverted in 45 patients (86.5%). These figures call attention again to the importance of the electrocardiographic pattern of low voltage, and flattening of the T waves with or without auricular fibrillation, as an extremely valuable clue in the diagnosis of chronic constrictive pericarditis. This point was well demonstrated in one of our own patients on whom various other diagnoses had been entertained until the electrocardiogram directed attention to a constricting pericardium as the underlying disease process.

L. *Other laboratory findings.* The venous pressure was determined in 36 of the patients, using the intravenous method, and was found to be greater than 150 mm. of water in 33; the readings were 110, 130, and 140 mm. of water respectively in the remaining 3 cases, still suggesting elevated readings. A significant anemia (less than 75% hemoglobin or 4 million red cells per cubic millimeter) was uncommon, being present in but 9 out of 51 patients on whom such hematological data are available. The total serum protein was assayed in 38 cases and was normal in 20, high (10.2 gm. per 100 cc.) in 1, and low (less than 6.0 gm. per 100 cc.) in 17. The albumin/globulin ratio was found to be definitely low (less than 1.2) in 4 out of 17 determinations.

2. **Results of Surgery.*** Surgical exploration with pericardiolysis and partial pericardiectomy was undertaken on 42 patients, 36 of whom were operated upon only once. Five patients were operated upon twice because of failure of the first procedure to improve their clinical status satisfactorily, and one patient has been operated upon three times. An anterior or anterolateral precordial incision was used in all cases, with the exception of one case in which a posterolateral incision was employed.[8]

* The first pericardiolysis and partial pericardiectomy in this series was performed in July 1928 by Dr. Edward D. Churchill, and he and Dr. Richard Sweet are together responsible for the gratifying results obtained in these cases.

Truly remarkable recoveries were made in 15 of the 42 patients thus operated upon, and they are regarded as having been essentially cured of their symptoms. Table 3 indicates the extent of this striking transformation, including the disappearance of all disabling symptoms and of almost all abnormal physical findings.

Another group of 10 patients showed definite improvement following operation: 8 are living, and 2 died six years following pericardiectomy. That surgery was of benefit to them is unquestioned, and, as may be seen in Table 4, their symptoms were ameliorated and the effects of pericardial constriction diminished.

There is one additional patient whose last operation took place less than 1 year ago. Although he is doing well, we have not included him in our follow-up figures, as we need a longer period of postoperative observation for accurate appraisal. The surgical approach in his case was unusual and has been made the subject of a separate report.

Satisfactory or excellent results have thus been obtained in 25 (60.9%) of the patients coming to operation.

Of the remaining 16 patients (Table 5), 6 died as the result of the operative procedure itself. Three of these succumbed on the operating table, 1 died one day postoperatively with pulmonary edema, 1 died of pulmonary embolism on the second postoperative day (he is the only case included in the series who was operated upon at another hospital), and 1 of bronchopneumonia and pulmonary edema 6 days after surgery.

Another group of 5 cases demonstrates death from complicating diseases. All survived the immediate effects of pericardiectomy but died from 1 month to 2 years later of illnesses which included acute pancreatitis, arterial embolism (following an omentopexy), empyema, pneumonia, and widespread sepsis. Four other patients died from 4 to 9 months after their operations from the effects of their underlying disease. The cause of death of 1 other patient, who died in another city 2 months after pericardiectomy, is not known.

3. **Status of Patients Not Operated Upon.** Seven patients were thought to be too ill for surgery, and all were treated medically in the hope that their clinical condition might improve to the point where the risk of operation was reasonable. All of these patients are now dead, a few months to 12 years after we had first examined them. Two of these were proved to have tuberculosis and the other 5 died in congestion.

The effects of the constrictive pericarditis were so minimal in 2 patients that surgery was thought to be unnecessary. One of these patients had mild symptoms for over 50 years and finally succumbed at the age of 76 (he has been reported extensively in a previous publication[3]); while the other had until recently been only mildly inconvenienced by the presence of palpitation secondary to auricular fibrillation.

One patient died in congestion before the operative series began, and another patient could not be traced.

4. **Pathological Studies.** A review of some of the findings at operation, as well as of the gross and microscopic findings on the 16 autopsied cases, throws considerable light on the extent of the pathological changes, the variety of tissues involved, and some of the reasons why surgical removal of portions of the anterior and anterolateral portions of the pericardium failed at times. It is to be remembered that these data come largely from the most severe examples of the disease.

TABLE 3. STATUS OF PATIENTS ESSENTIALLY CURED BY SURGERY

Case	Follow-Up Period (years)	Symptoms		Prominent Neck Veins		Liver Size		Edema		Ascites		Lungs		Present Activity
		Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	
P.C.	3	Dyspnea; edema; Abdom. discomfort	None	+	0	Enl.	Normal	+	0	0	0	Rt. hydrothorax	Normal	Normal life
J.K.	2	Dyspnea Abdom discomfort	None	+	0	Normal	Normal	0	0	0	0	Bilat. hydrothorax	Norma	Normal life
E.B.	1	Orthopnea; abdom. swelling; edema	Sl. dyspnea Sl. edema	+	0	Enl.	Normal	0	0	0	0	Normal	Normal	Normal life
R.C.	5	Abd. discomfort and swelling	None	0	Sl. dist	?	Normal	+	Sl.	+	0	Rt. hydrothorax	Normal	Normal life
T.P.	5½	Orthopnea; abdom. swelling; edema	None	+	0	Enl.	Normal	+	0	+	0	Normal	Normal	Normal life
A.T.	5	Palpitation; edema; abdom. discomfort	Some palpitation	+	0	Enl.	Normal	0	0	0	0	Normal	Normal	Normal life
E.S.	4½	Dyspnea; emesis; abd. swelling; edema	None	0	0	Enl.	Normal	0	0	+	0	Bilat. hydrothorax	Normal	Normal life
C.O.	18½	Orthopnea; abdom. swelling and discomfort	Sl. RUQ ache	+	0	Enl.	Sl. enl.	+	0	0	0	Bilat. hydrothorax	Normal	Normal life
B.K.	12½	Dyspnea Abdom. swelling	None	0	Sl. dist.	Enl.	Sl. enl.	0	0	+	0	Normal	Norma	Not known
L.L.	13	Dyspnea; abdom. swelling; edema	None	+	0	Enl.	Normal	+	0	+	0	Normal	Normal	Normal life
A.F.	13½	Dyspnea; abdom. swelling; edema	None	+	0	Enl.	Normal	+	0	0	0	Normal	Normal	Normal life
L.C.	13½	Abd. swelling	None	+	0	Enl.	Normal	0	0	+	0	Normal	Normal	Normal life
S.L.	5	Cough; edema	None	+	0	Enl.	*	0	0	0	0	Rt. hydrothorax	Pleur. thick. rt. base	Normal life
H.W.	6½	Dyspnea; abdom. swelling and ache; edema	None	+	0	Enl.	Normal	0	0	+	0	Rales	Dry Rales	Normal life
R.R.	1½	Nausea; emesis; leg pain; edema	None	+	0	Enl.	Normal	+	0	0	0	Normal	Normal	Normal life

* No data available.

TABLE 4. STATUS OF PATIENTS IMPROVED BY SURGERY

Case	Follow-Up Period (years)	Symptoms Pre-op.	Symptoms Post-op.	Prominent Neck Veins Pre-op.	Prominent Neck Veins Post-op.	Liver Size Pre-op.	Liver Size Post-op.	Edema Pre-op.	Edema Post-op.	Ascites Pre-op.	Ascites Post-op.	Lungs Pre-op.	Lungs Post-op.	Present Activity
D.G.	11	Fatigue Abdominal swelling and discomfort	Sl. dyspnea	+	Sl. dist.	Enl.	Normal	0	Sl.	+	0	Normal	Normal	Sedentary job
G.P.	6	Dyspnea Abdominal swelling	Some dyspnea	+	*	Enl.	Normal	+	+	?	0	Rales rt. base	Normal	Limited activity until death 6 yrs. later
P.C.	8	Abdominal swelling and discomfort Edema	Sl. dyspnea Palpitation	+	Sl. dist.	Enl.	Enl.	0	Sl.	+	0	Bilat. hydrothorax	Normal	Normal life
W.R.	6	Dyspnea; palpitation; abdominal discomfort	Sl. chest discomfort	0	0	Enl.	Enl.	0	0	0	0	Normal	Normal	Normal life
M.C.	3	Orthopnea Abdominal swelling Edema	None	+	Sl. dist.	Enl.	*	+	0	+	0	Bilat. hydrothorax	Left hydrothorax	Normal life
M.W.	1	Dyspnea; abdominal swelling and discomfort; edema	Some dyspnea	+	Dist.	Enl.	Enl.	0	0	+	0	Left hydrothorax	Normal	Limited activity
E.F.	3½	Dyspnea Abdominal swelling and discomfort	Palpitation Sl. edema	*	Dist.	Enl.	Normal	+	0	+	0	Bilat. basal rales	Normal	*
E.M.	3½	Orthopnea Abdominal swelling and discomfort	Sl. dyspnea	+	*	Enl.	*	+	0	0	*	Bilat. hydrothorax	Normal	Normal life
A.J.	1½	Orthopnea Abdominal swelling Edema	Some edema	0	Sl. dist.	Enl.	Sl. Enl.	0	Sl.	0	0	Rt. hydrothorax	Normal	Limited activity
O.P.	6	Dyspnea Abdominal swelling Edema	None while followed	+		Enl.	*	+	*	+	*	Rt. hydrothorax	*	Limited activity until death from pneumonia 6 yrs. later

* No data available

TABLE 5. STATUS OF PATIENTS UNIMPROVED OR ONLY TEMPORARILY BENEFITED BY SURGERY

Died on operating table (during first operation)	2
Died on operating table during second operation (status not materially improved by first operation)	1
Died in pulmonary edema 1 day postoperatively	1
Died of pulmonary embolism 2 days postoperatively	1
Died of bronchopneumonia and pulmonary edema 6 days postoperatively	1
Died of acute pancreatitis 1 month after second operation	1
Died of general sepsis 1 year postoperatively	1
Died of arterial embolism following an omentopexy (2 previous partial pericardiectomies had failed to improve his condition adequately)	1
Died of a type III pneumococcal empyema 1 year postoperatively, the symptoms and signs of cardiac tamponade having been much improved temporarily	1
Died of bronchopneumonia 2 years postoperatively, without having benefited significantly from surgery	1
Died 4, 6, and 9 months postoperatively, respectively, in congestion	3
Died 6 months postoperatively, ? due to complicating Addison's disease	1
Died 2 months postoperatively, cause of death not known	1
Total	16

At the time of operation the surgeon observed evidence of an active inflammatory process in the pericardium in 6 cases (the total number coming to surgery was 42). The note on one such patient mentions that "there were multiple small bleeding points and the entire surface of the heart presented the appearance of a subacute inflammatory process." In another instance the situation was complicated by "edema and rather recently appearing inflammatory reaction which fused the pleura and pericardium together . . . the pericardium was very adherent and the adhesions were much more vascular and a cleavage plane less easily found than in the average case of longer duration. . . ." Similar remarks were made in the records of 4 other patients. It is interesting that 4 of these 6 cases are now thought to have been cured by operation, and 1 has improved although 2 operations were required for relief.

The typical findings in the pericardium at operation on the other cases were those of extensive old fibrosis and scarring. The pericardium was thickened and tough and, as noted previously, at times contained calcium deposits; and the pericardial cavity in so far as it could be examined was usually obliterated. On resection of a portion of this constricting envelope, the surgeon often observed that the released auricles and ventricles filled more fully. It is clear that much of the epicardium, as well as the pericardium, was removed in certain cases, both because the two membranous layers were so fused that a plane of dissection between them could not be found and because removal of the epicardium itself was often a prerequisite to adequate diastolic filling.

Considering the condition of the pericardium as found at autopsy, we discovered that in only 2 instances did small, free, unobliterated pockets of pericardial cavity persist. In the other 14 autopsied cases the pericardial and epicardial surfaces had completely fused. The pericardium was thickened in all cases, the greatest thickness ranging from 3 to 20 mm., and in 11 of the specimens calcification was present. The extent of this calcium deposition is indicated in Table 6. It will be seen that all surfaces were involved in 4 cases, that calcified rings were found in 2, and that the pericardium overlying the chambers of the heart was variably affected in the remaining 5. In particular, the posterior aspect of the left ventricle—an area out of the reach of the surgeon from the anterior approach—was calcified in 8 instances. There was only 1 example of a fibrotic ring constricting the great veins as they entered the heart. It seems apparent from these findings that in some cases of constrictive pericarditis, removal of the anterior or anterolateral

portions of the pericardium alone may be inadequate to release auricular and ventricular action completely.

Another reason why certain patients with this disease may not achieve completely satisfactory clinical results following surgery is to be found in a study of the myocardium itself. In 4 patients the surgeon commented at operation upon the flabby or thin appearance of the heart wall. In 1 of these the sis was thus produced which probably explained the auscultatory evidence of mitral stenosis observed during life. Microscopic studies of the myocardium showed degenerative changes in 5 of the 16 so studied. Two of these showed relatively slight myocardial fibrosis. An interesting finding in a few of the cases was adventitial and perivascular edema and fibrosis due probably to an extension of the process in-

TABLE 6. EXAMINATION OF THE PERICARDIUM AT AUTOPSY

(16 Cases)

Thickened pericardium		16
Calcification of the pericardium		11
1) complete	1	
2) complete save for operative defect	1	
3) "extensive"	1	
4) small amount diffusely	1	
5) anterior, right lateral, and diaphragmatic surfaces	1	
6) entire left ventricle and right auricle	1	
7) left ventricle (anterolateral and part posterior aspect) and right ventricle	1	
8) posterior aspect left ventricle	1	
9) lateral and posterior surfaces of heart	1	
10) band around A-V groove	1	
11) ring around apex	1	
Complete obliteration of pericardial cavity		14
Fibrotic ring around venae cavae		1

friable character of the muscle was graphically described by the surgeon's note, which stated: "I was gently sponging in the depths over the right auricle with a moist cotton pledget in a Hartmann forceps. Suddenly to my horror the forceps plunged into the cavity of the heart and there was a profuse hemorrhage of dark venous blood." The bleeding was controlled, and the patient is now well. In another case the right ventricle was similarly ruptured but was patched with pericardium and the patient survived.

At autopsy it was found that calcification extended into the myocardium itself in 4 instances, in 1 case forming a solid core of calcium through the right ventricular wall appearing on the endocardium, and in the other 3 cases penetrating the left ventricle and impinging upon the mitral valve. In 1 of the latter cases a slight mitral stenoward from the thickened visceral pericardium.

The possibility has also arisen that the formation of scar tissue over the defect in the pericardium resulting from the partial pericardiectomy might reproduce the same constriction of the heart that was present prior to operation. There are 4 instances in which such scar tissue found at the time of postmortem examination may have been of significant effect. In 3* of these, dense fibrous tissue had replaced the area of pericardium which had been removed; in the fourth a moderate amount of scar tissue had formed. Regarding another patient, on whom 2 partial pericardiectomies were performed, the surgeon remarked at the time of the second procedure that "at the lower end of the incision considerable scar tissue bound the heart to the sixth costal cartilage. This was

* These 3 patients all died from complicating disease, but 2 of them appeared to have received definite benefit from surgery.

resected and in itself appeared to give considerably more freedom to the heart."

There are thus called to mind 4 conditions which may interfere with the success of a pericardiolysis and partial pericardiectomy: (1) incomplete removal of constricting pericardial tissue, (2) disease of the myocardium itself, (3) formation of constricting scar tissue over the defect in the pericardium (apparently a relatively insignificant factor), and (4) persistence of an active inflammatory process.

Adhesions extending from the pericardium into the mediastinum and involving the esophagus and other structures were found only twice.

Pleural involvement, with pleuritis at times completely obliterating a cavity, was discovered in 15 of the 16 autopsied cases. This pleuritis was bilateral in 13 and was limited to the right pleural cavity in 2 instances. A bilateral hydrothorax was present in 6 cases, a right hydrothorax in 2, and a left hydrothorax in 3. Active pulmonary tuberculosis was noted only once.

An abnormal liver was a characteristic finding in all 16 of these postmortem examinations. Four of the livers weighed more than 1600 grams, and a perihepatitis was present in nine. In 14 a definite cirrhosis was present and most of these were diagnosed as cardiac in type. Cardiac, or what Koletsky and Barnebee[5] prefer to call "congestive," cirrhosis supposedly results from long standing passive congestion. Although the early changes in this condition are limited to the central areas, varying degrees of portal fibrosis are usually present, accounting for a diagnosis of portal and unclassified cirrhosis in a few of the cases.

Most of the reports dealing with cardiac cirrhosis emphasize that the fibrosis may be limited to the central areas, but that in cases with very long periods of congestive failure the fibrosis is also portal, and the cases of constrictive pericarditis would fit into this latter group. The usual explanation for the portal fibrosis is that the chronic passive congestion produces anoxemia and thus makes the liver cells anywhere in the lobule more susceptible to injury.

In reviewing the liver sections in this series of constrictive pericarditis cases, it was apparent that portal fibrosis was quite prominent in most of the cases. In a few cases this was most marked in the parenchyma not far from areas of perihepatitis, and it is quite possible that the portal fibrosis is in part due to extension down from Glisson's capsule.

Another factor, and one that has not been emphasized before, although it is probably more important than the above-mentioned considerations, is the finding of marked intimal thickening with luminal narrowing, and in some cases definite thrombosis with recanalization, of the hepatic veins. This endophlebitis process due to long standing high venous pressure must have produced a mild Chiari syndrome leading to portal hypertension, portal fibrosis, and possibly additional ascites. Confirmation of this portal hypertension is found in the presence of splenomegaly in some of these cases. Most of the spleens weighed over 300 grams; three weighed 350, 430, and 600 grams respectively. Since some cases of unquestioned cardiac cirrhosis resulting from valvular heart disease have shown similar hepatic vein changes, it is believed that the cirrhotic changes (whether central or portal) in chronic constrictive pericarditis are the result of chronic passive congestion and can be legitimately called "cardiac" or "congestive" cirrhosis.

A perisplenitis was diagnosed in 9 cases, and there was a chronic peritonitis present in 3.

5. **Etiology.** In 56.5% of the patients of our series neither the history nor the laboratory studies gave a clue as to the etiology of the disease process. (Sections of the pericardium were available for microscopic study in 46 of our 53 cases.) The characteristic story was one of a gradual awareness of ill-health, coming on over months or years without an acute or otherwise remarkable illness initially. On reviewing the records, not only do we find the past history to be of no assistance but there is no evidence of unusual familial incidence of tuberculosis or rheumatic fever and no reference to close contacts with friends or relatives afflicted with these diseases.

A *tuberculous origin* was demonstrated in 9 patients (17.0%) either by guinea pig inoculation of the pericardial fluid or by pathological study of the pericardium. Three of these patients were females. A pericardiectomy was either performed or attempted on 7 of the 9, with one patient dying on the operating table, 1 dying the day after the procedure, 1 succumbing a month later to a complicating pancreatitis, and 1 dying 2 years later of pneumonia (minimal active pulmonary tuberculosis was present at autopsy also). Three patients are alive and well from 3 to 6 years after surgery. The other 2 patients died after a six month and a 2 year illness respectively, without attempt at operation (1 of these showed miliary tuberculosis at postmortem examination). Thus 6 of the group are now dead.

This group of 9 cases is too small for definite conclusions, but a few observations on the clinical and pathological findings may be pertinent. It may be significant that only 2 of these patients had been ill for as long as 2 years when first seen by us, and the others for only a year or less, whereas in the rest of the cases in the series 74% had noted their symptoms for 2 years or more. The infrequency of pericardial calcification and of cardiac arrhythmias is also of interest, these findings being noted only once each (and both in the one patient who had been ill the longest).* By contrast, 38% of the other 44 cases showed auricular fibrillation or flutter and 64% showed a deposition of calcium in the pericardium by Roentgen-ray examination or by pathological study. In only 1 case was there diagnostic evidence of active tuberculosis elsewhere than in the pericardium.

A review of the microscopic findings in the pericardial sections obtained at the time of autopsy or from surgical biopsy specimens from both tuberculous and nontuberculous cases disclosed two additional and important considerations. First, it is obvious that the diagnosis of tuberculous pericarditis may be missed if an inadequate number of tissue sections is studied. In 1 recent case extensive examination of numerous microscopic sections was required before clear cut evidence of tuberculosis was found. It is not hard to see how failure to select the right portion of pericardial tissue or to take additional sections from tissue blocks may result in a report merely of fibrosis or inflammation and fibrosis. Secondly, there is no sharp dividing line between the microscopic picture of healed tuberculous pericarditis and what may be called idiopathic constrictive pericarditis. In both conditions pericardial

* Since the above was written, another tuberculous case, a 23 year old patient of Dr. Conger Williams, has been seen at the Massachusetts General Hospital. He had been ill for 4 months with evidence of progressive cardiac tamponade and died a few hours after admission to the hospital. Postmortem study disclosed a thickened pericardium which did contain some calcium, and microscopic sections revealed tuberculous involvement of the pericardium and of the mediastinal nodes. No arrhythmia had been observed, and it is of interest that his illness was of such short duration.

fibrosis and at times chronic inflammatory changes with an infiltration of lymphocytes are present. In both, giant cells may be found, related to tubercle formation or to a foreign body reaction due to calcium deposition or to the two together. Figure 1 indicates the microscopic appearance of two areas of the pericardium of a tuberculous case, showing typical tubercle formation on the one hand and nonspecific changes (of the type usually

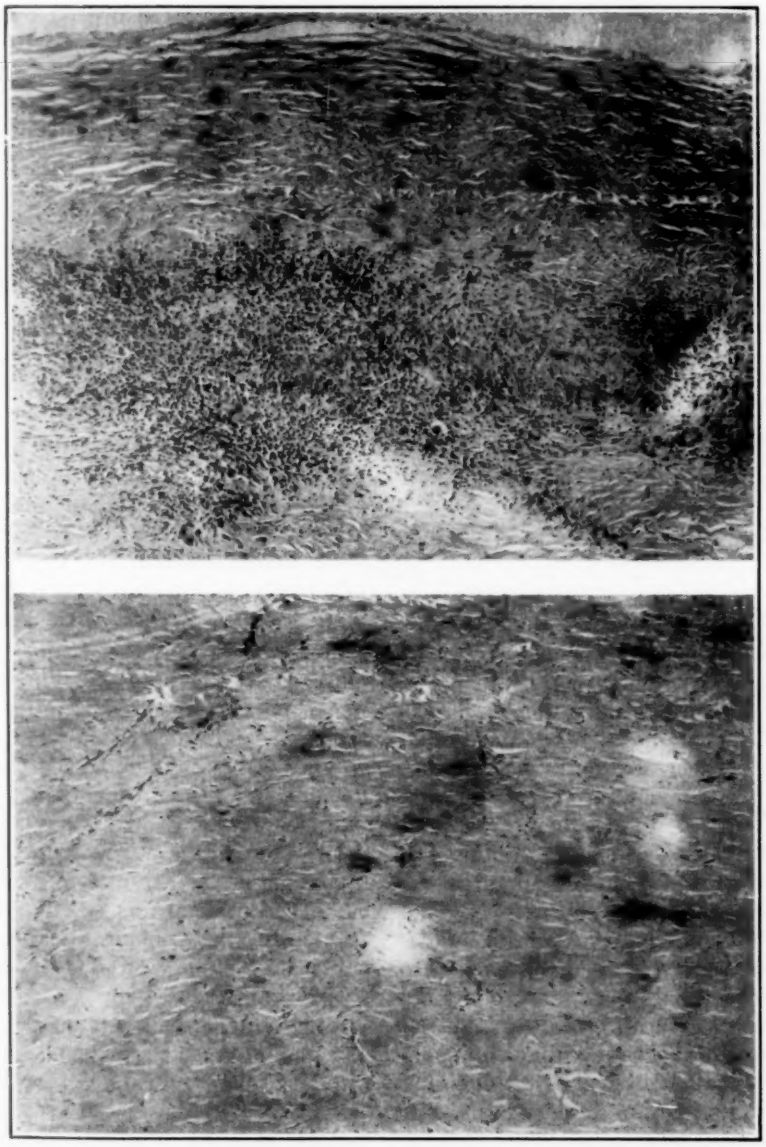

Fig. 1. Two sections of pericardium, both from a patient with tuberculous chronic constrictive pericarditis, showing diagnostic tubercle formation above and nonspecific fibrosis below. The latter is the characteristic finding in "idiopathic" chronic constrictive pericarditis cases.

encountered in "idiopathic" cases) on the other. It is important that in two cases healing tubercles were present in the operative specimens but no evidence of tuberculosis was found at postmortem examination 2 and 3 years later.

It is not easy to distinguish between healed tuberculous and healed "nontuberculous" constrictive pericarditis by history or by physical examination or by pathological study.

died at the age of 24 and was found at autopsy to have "chronic rheumatic endocarditis" with aortic stenosis. In no case, however, was there a history typical of rheumatic fever.

In 3 additional patients the past history contained highly suggestive, but not conclusive, evidence of a previous acute pericarditis. One of these patients had been acutely ill for 2 months with fever and pain in his precordial region 10 years prior to the onset of

Table 7. ETIOLOGICAL BACKGROUND

(53 Cases)

	Number of Cases		% of Total
Unknown		30	56.5
Tuberculosis		9	17.0
History of Acute Pericarditis		9	17.0
Previous acute pericarditis unaccompanied by other clinical abnormalities	4		
Previous acute pericarditis complicating:			
1) endocarditis with mitral murmurs, arthritis (with history of bilateral pneumonia and left plueral effusion 2½ years before); chronic rheumatic endocarditis and aortic stenosis at autopsy	1		
2) acute polyarticular rheumatism, endocarditis, myocarditis, bilateral hydrothorax	1		
Probable previous acute pericarditis with:			
1) 4-day illness at age of 16 months diagnosed as probable pericarditis	1		
2) episode of anterior chest pain, nausea, vomiting, diagnosed as coronary thrombosis	1		
3) 2-month febrile illness with precordial chest pain	1		
Miscellaneous		5	9.5
Pleurisy preceding onset of chronic symptoms	2		
Pneumonia preceding onset of chronic symptoms	1		
"Influenza" preceding onset of chronic symptoms	1		
History of "water on stomach and large liver" during a febrile illness of 2 months' duration 7 years prior to onset of chronic symptoms	1		
Total		53	100.0

A history of a *previous acute pericarditis* was obtained in 6 of the 53 cases. In this group there were 4 patients in whom an illness consistent with acute pericarditis alone, without major involvement of other structures, was described. In 3 of these, symptoms suggesting pericardial constriction followed soon after the initial acute involvement, but the patients did not come to us for treatment for 4, 2, and 1, years respectively. In the fourth case there was a 29 year period of good health after acute pericarditis followed by 2 years of dyspnea and ankle edema before we saw him. In the remaining 2 cases pericarditis was merely one complication of a more diffuse disease process, as indicated in Table 7. The latter group includes a patient who

his symptoms. Another had been hospitalized because of an illness with sharp pain across his anterior chest associated with nausea and vomiting, which was diagnosed as coronary thrombosis; in retrospect it appears that the probable correct diagnosis was acute pericarditis. The third patient was thought by her own physician to have had pericarditis at the age of 16 months, but a definite diagnosis was not made; shortly after this episode she developed the symptoms and signs of a chronic cardiac tamponade.

None of these patients was proved to have tuberculosis, pericardial or otherwise, and the causative factor or factors in their original pericarditis remains uncertain. In particular, we are not impressed by the evidence for

a rheumatic background to the group as a whole. Three of these 9 cases with a history of initial acute pericarditis are now living; pericardial calcification was found in 5 of them, and 3 showed auricular fibrillation.

Finally, mention should be made of 2 patients who gave a history of pleurisy ("without pericarditis") during the few months prior to the onset of their chronic symptoms and of an additional 2 patients whose initial acute illnesses were diagnosed as pneumonia and influenza respectively. There is, moreover, 1 patient who is said to have had smothering attacks, "water on her stomach and a large liver" during a febrile illness of 2 months' duration 7 years prior to the onset of her chronic symptoms. This could certainly have been acute pericarditis with effusion.

It is obvious that many of these patients had more than one type of serous membrane involved and that a polyserositis did in fact exist, idiopathic in origin. Such a designation is broadly inclusive and has a descriptive value; it does not, however, help to elucidate the nature of the disease process.

6. **Discussion.** That orthopnea is not one of the commoner symptoms in chronic constrictive pericarditis should not obscure the fact that shortness of breath itself is the most frequent complaint which these patients have. As we have seen, not only does it occur more often than any other symptom but also it is found most frequently as the initial complaint. Our investigations tend to rule out a concomitant hydrothorax, a high diaphragm from ascites, or the presence of auricular fibrillation or flutter as the significant factor, and point rather to constriction of the heart itself as being a most important element in its production. We have observed clinically that an increase of the intensity of the second pulmonic sound is often present as an indication of an increased pressure in the pulmonary arterial system.

We have also noted at autopsy that the left ventricle (as well as the rest of the heart) undergoes constriction and that the pericardium overlying it is frequently calcified. It is logical to assume that in most patients with constrictive pericarditis it is the whole heart which is affected and not merely, or even predominantly, the chambers of the right side.

It is also important to stress the fact that the heart is not necessarily normal in size in constrictive pericarditis. Moderately large hearts occur in about one third of the cases, and occasionally even a very large heart is found. More valuable than determination of the heart size are Roentgenographic observations of the presence of pericardial calcification and the character of the cardiac pulsations. These studies, plus the electrocardiographic pattern previously described, are among the most helpful diagnostic tools, although they do not supplant a well taken history and a careful physical examination.

In many of our cases surgical removal of pericardium overlying the anterior surface of the heart, together with a lysis of lateral and apical adhesions, was adequate to relieve the mechanical embarrassment and allow essentially normal systolic contraction and diastolic filling. In a minority of the cases this procedure alone was not enough, and with this experience we anticipate that a more generous pericardiectomy will have to be performed at times in future patients if satisfactory results are to be achieved. The operation is not to be undertaken lightly, for these patients are often in a "poor risk" group and a single procedure may not be enough. As we have seen, the myocardium itself may be involved, in addition to disease of the pericardium, pleura, and liver. A

skilled surgeon is required, and close co-operation between him and the attending cardiologist is a prerequisite to success. It is probably wise to reserve operation for those patients whose symptoms significantly limit their activities and to treat by medical measures alone those who have only a minimal disability, especially if they are in the older age group.

Study of the etiological background of our cases provides an unsatisfactory answer to the questions: What is the cause of chronic constrictive pericarditis? Are all these patients suffering from the same disease? Are they all tuberculous in origin?

Harvey and Whitehill[4] state that of 17 patients with tuberculous pericarditis without effusion, 5 developed a clinical picture consistent with chronic constrictive pericarditis (all 5 died). More recently, Pickering[6] in London observed 16 cases of tuberculous pericarditis and has found that 14 of them progressed to the stage of pericardial constriction, 7 coming to surgery. Edwards[2] in Liverpool has also followed 8 patients with proved tuberculous involvement of the pericardium and has seen all of them develop the clinical picture of chronic constrictive pericarditis. The reported incidence of tuberculosis in patients suffering from chronic constrictive pericarditis itself varies: Blalock and Burwell[1] made a diagnosis of tuberculosis in 18 of their 28 cases; Pickering encountered 11 cases of chronic constrictive pericarditis (not drawn from the group of tuberculous pericarditis mentioned above) and believed that all but 1 were tuberculous in origin although actual proof was lacking.* These and other reports, as well as our own data, emphasize that both tuberculous and chronic constrictive pericarditis predominate in males, and that the onset of tuberculous pericarditis may be so insidious as to escape early detection. It is also clear that isolation of tubercle bacilli from pericardial, pleural, or peritoneal fluid is not readily accomplished.

Our small group of 9 proved tuberculous cases seems, as we have pointed out, to have an unusually short period of ill health, which to some extent distinguishes them from the rest of the cases in the series and which may explain the infrequency of cardiac arrhythmias and of pericardial calcification. We wonder why the other 44 patients with idiopathic constrictive pericarditis did not show signs of tuberculous involvement of other organs at some time; and we also wonder why pathological study of the pericardium was unrevealing in so many cases (although we have commented upon some possible reasons therefor). It may be postulated that these cases represent an old, burned-out tuberculous pericarditis analogous to an old tuberculous pleurisy, and hence that as in the latter condition microscopic study might not disclose typical tubercle formation. Evidence of an active inflammatory process was found at the time of operation on 6 patients, however, and in only 1 of these was the diagnosis of tuberculosis made by pathological examination of the section of pericardium removed. Although we believe that the theory of the tuberculous origin of essentially all cases of chronic constrictive pericarditis has much to recommend it, we are not able from our own studies as yet to state without reservation that other etiological factors may not also be important.

Summary. 1. In the period 1914 through May 1947, 53 patients with constrictive pericarditis have been seen

* It should be mentioned that the differing incidence of proved tuberculous infection of the pericardium at the Massachusetts General Hospital and at other medical centers may be explained in part by differences in geographical location and type of patient seen.

at the Massachusetts General Hospital or in the private practice of one of us (P.D.W.). 2. Shortness of breath on effort was the commonest symptom and was followed in incidence by swelling of the ankles and legs, abdominal swelling, and abdominal discomfort. 3. The most common physical findings were, in order of their frequency, enlargement of the liver, prominence of the neck veins, ascites, peripheral edema, and signs of fluid and/or pleural thickening at the lung bases. 4. Cardiac enlargement (as determined by Roentgen-ray observations) was present in 29 cases (54.7%), and by fluoroscopy the cardiac pulsations were found to be diminished or absent in 32 of 40 patients so studied. Chest films also disclosed evidences of a unilateral or bilateral hydrothorax in 28 patients (52.8%). 5. Calcification of the pericardium was observed in 29 cases (54.7%). 6. Electrocardiograms were taken on 52 of the 53 patients and showed auricular flutter or fibrillation in 20 (38.5%), low voltage in 17 (32.6 %), and abnormal T waves in the limb leads in 45 (86.5%). 7. Surgical exploration with pericardiolysis and partial pericardiectomy was undertaken on 42 of these patients. The results in 25 (60.9%) have been satisfactory. Six patients died as a result of the operative procedure itself, 5 died from complicating diseases, and 4 died from the effects of their underlying disease. The cause of death of 1 patient is not known. 8. Seven patients were too ill for surgery and died while receiving medical treatment. One patient died before the operative series began, 2 patients had such minimal symptoms that operation was felt to be unnecessary, and 1 patient has not been followed. 9. The etiology was entirely obscure in 30 cases (56.5%) despite the fact that sections of the pericardium were available for microscopic study in 46 of the 53 cases in the series. Tuberculous involvement of the pericardium was proved in 9 (17%). Healed (fibrous) scarring was the usual finding and this may or may not have resulted from tuberculous infection. A history of acute pericarditis of unknown origin was present in 6 cases (11.3%), and in 3 others (5.7%) the history was very suggestive of an episode of acute pericarditis in the past.

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CHRONIC CONSTRICTIVE PERICARDITIS OVER THE LEFT HEART CHAMBERS AND ITS SURGICAL RELIEF

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A new development of importance in the diagnosis and treatment of chronic constrictive pericarditis in this country took place in the operating room in 1928 when a young woman, crippled by chronic constrictive pericarditis, was cured by surgery. This ushered in a new era which, during the past 20 years, has in large part fulfilled the hope originally raised. However, there have been difficulties particularly in the surgical relief of the minority of more obstinate cases. Surgical approach through the anterior wall of the chest was successful in the majority of those patients operated upon, but here and there were failures despite such operations even when they were repeated in the same cases.[1,4,5,6] During the past few years light has been thrown on at least one of the reasons for our occasional earlier failures and it is of this that we now write. We shall report 3 of our interesting and puzzling cases together with the methods used in deciding their future course.

Case Reports. Case 1. J.N., male aged 16, was referred to us from Oklahoma on August 8, 1932, with the diagnosis of chronic constrictive pericarditis. In early childhood he had had chicken pox and measles; at 5 years of age a tonsillectomy was done. At 9 years he had "double pneumonia" and was in bed for 6 weeks. There was a complication of left pleural effusion and this was tapped. Cardiac enlargement and a systolic murmur were discovered then. At the age of 13 a routine examination showed some cardiac enlargement with a systolic murmur, pulsating veins in the neck and enlargement of the liver the edge of which was felt three finger-breadths below the costal border.

When 14 years old, during the winter of 1929-30, he noticed that his face was swollen and that he had some difficulty in getting on his waistcoat due to enlargement of the abdomen. Edema of the thighs was developing at that time and the liver was enlarged until its lower edge reached the umbilicus. He continued at school part-time for a year and then had to give up and was living a semi-invalid life when we saw him first at the age of 16. He had had very little dyspnea. Diuretics were used with temporary benefit. Two months before entrance to the Massachusetts General Hospital his abdomen had been tapped

and 8 liters of fluid removed. It should be stated that digitalis had been ineffective. There was nothing abnormal in the family history.

Physical examination showed a well developed and moderately well nourished young man lying comfortably in bed without dyspnea but with slight to moderate engorgement and pulsation in the jugular veins. The heart rhythm was absolutely irregular at a rate of 120 and the pulse was definitely paradoxical. The blood pressure was 110 mm. systolic and 95 diastolic. The heart showed moderate enlargement. The sounds were of fair quality. There was a loud blowing systolic murmur at the apex; there were no diastolic murmurs. A slight third sound was heard at the apex. The lungs were clear. The abdomen was uniformly prominent. There was slight edema over the anterior abdominal wall and over the shins. The heart shifted definitely on change in position of the thorax. The liver edge was not tender; it was easily felt extending across the abdomen half way between the umbilicus and the costal border. There was no Broadbent's sign, clubbing of the fingers, or pyrexia. The blood was normal. The urine showed the slightest possible trace of albumin with a rather high specific gravity due to restriction of fluid intake. Roentgen-ray examination showed definite enlargement of the heart shadow in all diameters, particularly in the region of the auricles. There was an increase in the supracardiac shadow thought to be due to venous congestion. Barium in the esophagus showed deviation to the right in the region of the left auricle. Pulsations were weak. The lung hilus shadows were increased and the pleurae were markedly thickened on both sides. The electrocardiogram showed auricular fibrillation at a ventricular rate of 80 with slight right axis deviation and inverted T waves in leads 2 and 3.

Pericardial resection was advised and on September 27th, 1932, this was done by Dr. Churchill,[2,7] utilizing the anterior approach. A very much thickened pericardium with some calcium deposit was found and dissected from the right ventricle and the right auricle and in part from over the left border of the great vessels. A considerable portion of the diaphragmatic pericardium extending backward to the region of the inferior vena cava was removed. A considerable amount of calcified pericardium was left but the amount that was excised allowed the heart to herniate outward and greatly increased its diastolic filling. Microscopic examination of the pericardium which was removed showed hyaline degeneration of fibrous connective tissue with focal deposits of lime salts.

His postoperative condition was satisfactory but improvement was slow. In the course of the first week the anasarca seemed to be clearing somewhat and the cervical veins were less engorged. The venous pressure dropped from 28 cm. to 14 cm. After disappointingly slow progress and the use intravenously of mercurial diuretics on several occasions and abdominal paracenteses he returned to his home in Oklahoma where he remained 10 months. He returned in September 1933, showing considerable improvement but not adequately relieved. He had lost about 20 pounds in weight but still required an occasional abdominal paracentesis. The serum protein was 4.3 gm.% The liver function showed a 10 to 15% retention of the dye. His electrocardiogram showed auricular fibrillation with slightly low voltage and slight right axis deviation as before. Roentgen-ray examination showed some calcification which had not been definitely evident before. It was thought that further pericardial resection was indicated.

On November 16, 1933, Dr. Churchill[2] operated again with ease through the original scar which was excised. Calcified pericardium at the base of the great vessels was removed and the right ventricle was more completely freed. The left auricular appendage was dissected free. The pericardial tissue removed showed as before fibrosis with calcification. There was an uneventful recovery after this second operation but no further improvement, and on March 30, 1934, a Talma operation (omentopexy) was done because of the opinion that the liver con-

dition was now possibly responsible for the persistently recurring ascites. At the time of his operation a small bit of liver was removed and was found to show slight cardiac fibrosis. The liver capsule was not thickened (no frosting or Zuckergussleber). The boy's postoperative course was uneventful. It is doubtful that the omentopexy was followed by a real improvement in the patient's general condition.

The succeeding 18 to 24 months were devoted to dietary therapy and experimentation. The amount of fluid intake together with the salt intake was varied to observe if any changes in fluid retention might occur. It may be noted that after the institution of dietary restrictions the number of necessary abdominal paracenteses was reduced significantly. Prior to the dietary changes the patient was tapped at least once a week with a yield of between 6000 and 9000 cc. at each occasion. After a low salt and low fluid intake regime was observed for a sufficient length of time it was necessary to tap the abdominal cavity only once every 3 weeks with a yield well under the original 9000 cc. The relationship between salt and fluid intake and fluid retention in the serous cavities and peripheral tissues was apparent.

The patient's condition remained relatively satisfactory until December 19, 1940, at which time he suddenly became aware of a numbness of both legs below the hips. Both feet were very white, cold and dry. Femoral pulsations were lacking. Cardiac examination revealed no definite change from the previous record; auricular fibrillation was still present. A right and left common iliac embolectomy together with a right femoral embolectomy were performed immediately with a return of the right femoral pulsations. Large emboli were removed from all three arteries. Postoperatively the use of anticoagulants, Pavaex boots and a lumbar sympathetic block seemed of no benefit. The patient's condition gradually became worse; both legs became more and more discolored and he complained of tingling in the left leg and no sensation in the right. On December 22, 1940, while attempting to turn over in bed he became extremely short of breath, gasped and expired.

"**Necropsy:** The body is that of a well developed well nourished 25 year old man measuring 171 cm. in length and weighing 145 pounds. There is an old semicircular well healed precordial incision measuring 18.5 cm. in length. The anterior portion of the left fourth, fifth and sixth ribs as well as a portion of the sternum are absent. There is also an old well healed right upper quadrant paramedian incision measuring 4 cm. Pitting edema extends up both legs to just above the knees. The scrotum is enormously enlarged, measuring 20 cm. in diameter, and is soft; a fluid wave is easily demonstrated. The muscles are red brown and negative.

"*Peritoneal cavity* contains about 1000 cc. of this yellowish fluid. The peritoneum itself is markedly thickened, tough and fibrous. It measures in some places 5 mm. in thickness. *Appendix, esophagus* and *stomach:* essentially negative. *Intestines* show moderate distention. *Retroperitoneal* glands negative. Margin of the *liver:* the liver edge is 2 cm. below the costal margin in the right midclavicular line and 4 cm. below the zyphoid. Diaphragm: right side at fifth interspace; left at sixth rib.

"*Pleural cavities:* the right pleural cavity contains about 2000 cc. of thin straw colored fluid. Extending between the right lower lobe and diaphragm in the medial and posterior part are numerous thick fibrous smooth adhesive bands resembling enlarged chordae tendineae and measuring up to 2 to 3 mm. in diameter. The left pleural cavity contains 500 cc. of similar fluid. The left upper and lower lobes are densely adherent to the parietal pleurae and separate with only the greatest difficulty. Trachea, bronchi and bronchial glands: negative. *Lungs:* the right lower lobe is moderately firm throughout and on section numerous hemorrhagic foci 3 to 6 mm. in diameter are found. Near the costophrenic angle the hemorrhagic areas are confluent and suggest bronchopneumonia rather than infarction. Similar but

less extensive foci are seen in the left lower lobe. The openings of the pulmonary veins are free from thrombi.

"*Mediastinum* and *pericardium:* on removing the chest plate the tissue underlying the previously mentioned scarred area is found to be tough and fibrotic. An area measuring approximately 6 by 5 cm. of the lower anterior portion of the pericardium has been surgically removed. In its place is a moderate amount of fibrous scar tissue which is adherent to the under surface of the operative wound, but which separates easily with blunt dissection. The remaining portion of the anterior parietal pericardium is for the most part fibrous and adherent to the visceral layer. The upper two-thirds of the left antero-lateral portion of the pericardial cavity is completely inseparable and obliterated by irregular confluent masses of calcium, extending cephalad to involve the base of the aortic valve and forming a large plaque measuring 9 by 6 cm. in extent. The outer surface of this plaque is covered by fibrous tissue which in turn is adherent to the mediastinal parietal pleura of the left lung. This plaque extends somewhat posteriorly to impinge by external pressure upon the lumen of the mitral valve. There is no calcification of the pericardium in the region of the apex of the left ventricle. There is a similar but somewhat smaller zone of pericardial calcification involving the antero-lateral aspect of the right ventricle over an area measuring 9 by 4 cm. On this side however, the calcification extends almost to the apex of the right ventricle but not as high up as the level of the pulmonary artery. Posteriorly the pericardium is free of calcification.

"*Heart:* The heart is not dissected free from the pericardium and lungs but opened in situ. The myocardium is red brown. The right ventricular wall thickness measures 3 to 4 mm.; the left, 13 to 15. The left auricle is enlarged; its cavity measures 8 by 6 by 4 cm. The remaining cavities and columnae carneae are essentially negative. The lateral aspect of the mitral valve is pressed on externally by the calcified pericardium resulting in definite mitral stenosis. The aortic valve is moderately thickened and shows slight but definite interadherence of the cusps at their commissures. The other valves are essentially negative. The coronary arteries are negative.

"*Aorta:* The thoracic and abdominal aorta is normal. The right common iliac artery and its branches show no evidence of obstruction due to secondary thrombosis or emboli. The arteriotomy wound is plainly visible and well nealed. Dissection of the common femoral on the right shows an embolus at its bifurcation which obstructs both the superficial and the profunda femoral vessels. There is a secondary clot extending into the superficial femoral for an indeterminate distance. The profunda femoral on the other hand is plugged with a secondary thrombus for only a short distance. On the left there is an extensive thrombosis in the external iliac artery with thrombosis at the site of the arteriotomy wound of the common iliac artery. Thrombosis also extends into the left hypogastric artery. This thrombosis extends down to the origin of the deep epigastric artery where it stops. There seem to be areas of old thrombus formation in this area of blood clot suggesting that all the emboli had not been removed at the time of operation. This also would be borne out by the fact that following the removal of the embolus of the left common iliac artery there was no back bleeding from the external iliac artery. Dissection of the left common femoral artery shows another embolus at the bifurcation with a secondary thrombus formation extending into both the deep and superficial femoral arteries.

"*Pulmonary artery:* normal.

"*Vena cava:* The inferior vena cava is greatly dilated, measures 2.6 cm. in diameter, and at its diaphragmatic opening easily admits two fingers throughout the entire extent.

"*Diaphragm:* Is markedly thickened and measures up to 0.8 cm. in thickness. The inferior surface is coated with icing and also shows a trabeculated aspect near the crux. This is most marked on both sides of the round ligament.

Liver: Weighs 1400 gm. Most of the anterior and diaphragmic surfaces of the liver are covered with icing. Its entire surface is irregular and nodular, the nodules measuring up to 1.3 cm. in diameter. On section it is extremely tough and fibrous, being light red brown in color. Bile ducts: Normal. *Pancreas:* Is encased in tough fibrous peritoneum. *Spleen:* Is moderately fibrous and is covered in spots by grayish white tough icing. It is estimated to weigh 350 gm.

"*Adrenals:* Normal. *Kidneys:* Weight 275 gm. In the lower pole of the right kidney is a mottled red and white area measuring about 9 cm. in diameter. On section this area is soft and extends well down through the cortex. The cortex measures 7 mm. The pelves are normal. Ureters, bladder, and prostrate: Normal. *Scrotum:* There are large bilateral indirect inguinal hernias extending far down into the scrotum and containing thin straw colored fluid. *Bone marrow:* red. *Brain:* essentially normal.

Microscopic Examination: *Heart:* A section taken through the heart and pericardium shows the very markedly thickened pericardium adherent to the myocardium, there being only a thin line of areolar tissue separating them. This plane of cleavage is penetrated at frequent intervals by fibrous strands which extend down into the myocardium. The myocardium itself shows a slight increase in fibrous tissue which separates the muscle bundles.

"*Lungs:* Lung tissue through the right lower lobe shows extensive pleural fibrosis beneath which are focal areas of atelectasis. The hemorrhagic foci noted grossly vary in structure. Some show merely alveoli filled with fluid, others with red blood cells and a few with occasional polymorphonuclear leukocytes. Although those containing the red blood cells are slightly suggestive of infarction the presence of intact alveolar walls and their irregular shape are more in keeping with focal hemorrhage.

"*Liver:* The capsule is tremendously thickened and fibrotic and in one area a liver lobe has been entirely surrounded. The remainder of the liver shows an increase in the interlobar fibrous tissue.

"*Pancreas:* Dense fibrous tissue surround the pancreas which it itself normal.

"*Spleen:* Splenic capsule is markedly thickened and fibrotic.

"*Kidneys:* A section through the area of the lower pole of the right kidney noted in the gross shows early necrosis of the tissue. There is infiltration of the tissue by polymorphonuclear leukocytes and considerable cellular debris. In a few places the normal architecture is partially destroyed, leaving mere shadows of tubules and glomeruli. Other sections of the kidney show slight congestion.

"*Necropsy Diagnosis:* Adhesive constrictive pericardits with calcification; embolism, left common iliacs; anasarca; peritonitis, chronic fibrous, generalized; pulmonary edema; renal infarct, right; operative wounds; left lower paramedian; right inguinal recent; right upper quadrant paramedian left; pericardiolysis; peripheral edema; ascites; perihepatitis and perisplenitis, chronic; endocarditis, chronic rheumatic with stenosis, aortic and ? mitral; dilatation of the venae cavae; hydrothorax bilateral; pleuritis, chronic fibrous, bilateral; pleuropericarditis, chronic left; cirrhosis of the liver, cardiac."

Comment: This was one of our earlier experiences with the vicissitudes of the treatment of chronic constrictive pericarditis. Although the patient was somewhat helped by surgery the result was still quite unsatisfactory. As seen in the report of the necropsy examination the amount of constricting calcified pericardium still present could readily account for the presenting symptoms and signs by virtue of the compression of the left heart chambers. The existence of the prominent pulmonary second sound was evidence against the presence of an atonic right ventricle. Even at that early date the importance of the salt intake in relation to the degree of fluid accumulation was shown by the results obtained with variations in the diet. A few of the presenting problems might have been answered if at that time cardiac catheterization had been avai!-

able as a diagnostic procedure, as will be demonstrated in the following two cases.

Case 2. R.P., male, aged 21 years, was referred to us from western Pennsylvania on September 15, 1944, with the diagnosis of chronic adhesive pericarditis. His early childhood was uneventful except for scarlet fever at the age of 7 years. We could obtain no familial history of tuberculosis. In March 1943, he was rejected for duty in the armed services because of the findings by routine Roentgen-ray examination of the chest consistent with the diagnosis of chronic calcific pericarditis. Although asymptomatic he consulted his local family physician who found his electrocardiogram compatible with the diagnosis of constrictive pericarditis and referred him to the Massachusetts General Hospital for treatment.

Physical examination revealed a well developed and well nourished young man in no distress. His blood pressure was 102 mm. mercury systolic and 80 diastolic. His pulse was regular at a rate of 80 and was paradoxical. The neck veins were not pulsating. Both lung fields were clear. The heart was not enlarged to percussion. The sounds were of good quality. The pulmonary second sound was greater in intensity than the aortic second sound. There were no murmurs and no third heart sound could be heard. The abdomen was not distended nor was liver or spleen enlarged. There was no evidence of peripheral edema.

Venous pressure on admission measured 117 mm. water (Burwell end point; normal upper limit). The total serum protein was 7.4 gm. per 100 gm. Both blood and urine were normal. The electrocardiogram by virtue of the inverted T waves in all leads was consistent with the diagnosis of constrictive pericarditis. Roentgen-ray examination of the chest revealed a calcified pericardium and evidences of old pleurisy at the left base with a very small amount of fluid in the right pleural cavity.

On October 6, 1944, Dr. Richard Sweet performed a pericardiectomy using the anterior approach. The entire anterior portion of the pericardium including a calcified band 1½ inches in width opposite the auriculoventricular groove was removed. This band also extended around and behind the apex. The patient's postoperative course was uneventful. On the day of his discharge (October 28, 1944) his venous pressure was, however, slightly elevated as shown by the venous pulsations in the neck extending 2 to 3 centimeters above the right clavicle. Fluoroscopy revealed relatively little change in the heart size. The cardiac pulsations remained poor. Both lung fields were hazy. In spite of these findings it was felt that the progress of the development of congestion might have been halted and that with further convalescence a more complete recovery might ensue.

During 1945 the patient's condition was fairly satisfactory. His venous pressure, however, remained elevated. Small rations of digitalis were prescribed to increase the tone of the right ventricle. Physical examination remained essentially unchanged. The electrocardiogram showed some improvement in the height of the T waves which were, however, still abnormal. The patient did light secretarial work throughout the year with no difficulty. We believed that there was still some pericardial constriction and calcification together with right ventricular atony.

On June 5, 1946, the young man again was admitted to the Massachusetts General Hospital. His was a history of progressive increase over a 2 to 3 month period of the size of his abdomen, shortness of breath, and increase in weight. He had been admitted to his local hospital for the treatment of an episode of acute congestion apparently secondary to tachycardia due to a change of rhythm from normal to that of auricular fibrillation. The physical findings of note included an increase in the venous pulsations in the neck (venous pressure of 265 mm. of water), rales at both lung bases with a question of an increase in the amount of fluid at the right base, cardiac enlargement with sounds of fair quality but with the pulmonary second sound of greater intensity than the aortic second sound, and a slightly enlarged tender liver.

Peripheral edema was also noted at times. His blood pressure was 108 mm. mercury systolic and 84 mm. diastolic and the heart rate was grossly irregular at 82. The Roentgen-ray film of the chest showed an increase in the heart size together with extensive calcification of the pericardium. The electrocardiogram confirmed the presence of auricular fibrillation and showed no improvement in the T waves; there was a change in axis deviation toward the right. Blood and urine examinations were within normal limits. The total serum protein measured 7 gm. per 100 gm.

On June 20, 1946, Dr. Richard Sweet performed the second pericardiectomy, the site of the original incision being used again. On this occasion a constricting band of calcified pericardium was removed from the area of the right auriculoventricular groove. The right ventricle was seen to fill more rapidly thereafter and the blood pressure rose. Once again the patient's postoperative course was uneventful. Although a little short of breath on discharge on July 13, 1946, he seemed much improved clinically. The venous pressure then measured 200 mm. water.

While at home he adhered strictly to a medical regime consisting of a low salt diet, digitalis, ammonium chloride and intravenous mercupurin as needed. Within a month of his return home, however, his original symptoms recurred.

On December 10, 1946, he returned to the Massachusetts General Hospital. He was obviously much worse. Shortness of breath was noted even while he was lying in a semi-erect position in bed. His cough was persistent. The neck veins were very prominent and pulsating, with venous pressure of 300 mm. water. There was evidence of fluid at both lung bases. Cardiac enlargement was apparent and the heart sounds were mediocre in quality. A paradoxical pulse was present with rhythm irregular at 82. The blood pressure was 108 systolic and 76 diastolic. There was a third sound at the apex without murmurs. The pulmonary second sound was of greater intensity than the aortic second sound. The liver edge was felt 7.5 cm. below the costal margin and was slightly painful to palpation. There was slight to moderate edema of the ankles bilaterally.

Future management of this case demanded that we determine which of the following factors was most important in causing the persistence of the congestion and that we govern any further surgery with this in mind:

1. Obstruction to the entrance of blood into the heart through mediastinal constriction of inferior and superior venae cavae and of the right auricle.

2. Failure of an atonic right ventricle which had been very probably involved in a subepicardial myocarditis in the development of the chronic constrictive pericarditis.

3. Constriction of the left heart chambers or of the left auriculoventricular groove acting like mitral stenosis to cause chronic right heart failure.

We decided to use cardiac catheterization as a diagnostic aid in determining the pulmonary arterial pressure. Dr. Lewis Dexter[3] kindly made this test for us and in demonstrating a three-fold increase above the normal of the blood pressure in the pulmonary circulation confirmed our clinical impression of constriction of the left heart chambers as indicated by accentuation of the pulmonary second sound and by the shift in the electrocardiographic axis towards the right. The pulmonary arterial pressure was found to be 72 mm. mercury; the normal averages 25 mm.

With this fact as a guide the surgeon could thus focus his attempts at decortication of the left auricle and left ventricle primarily, creating an adequate exposure by using the transthoracic or thoracotomy approach. On January 17, 1947, after the optimum preoperative condition was reached by medical measures a third pericardiectomy was performed by Dr. Richard Sweet. The left transthoracic approach was utilized. The pericardium was released from the apex, and the area behind the left auricle and left ventricle was released from the diaphragm and as far around in back as the inferior pulmonary vein.

Superiorly it was freed over the auriculoventricular groove and the auricular appendix of the auricle. A very wide liberation of the left ventricle and the left auriculoventricular septal groove was accomplished. Dr. R. H. Sweet's operative note was as follows:

"A long oblique incision was made starting in front close to the previous pericardiolysis incision, extending laterally under the breast and up beneath the pectoral fold as far as the midaxillary line. This incision was enlarged through the 6th interspace and on inserting a rib-spreader, after freeing the adhesions of the lung, an excellent exposure was obtained. The lung was densely adherent to the parietal pleura both beneath the ribs and along the mediastinal surface. The mediastinal adhesions were separated and the lung was retracted posteriorly and laterally. This gave an excellent exposure to the left posterior aspect of the pericardium. The phrenic nerve was identified and held aside with a retractor. The previously denuded section of heart appeared to be functioning well. This included the right ventricle and a very small portion of the left. The apex had been freed previously, but there had been considerable re-formation of constricting fibrous tissue in this region. This was freed and the remainder of the pericardium, which enveloped and held in a constricting vise the left ventricle, was released with moderate difficulty. It was adherent almost everywhere, however, by very dense adhesions, in some of which were actually plaques of very thick calcium requiring cutting with heavy scissors, but it was possible by freeing them to release the left ventricle completely all the way around behind. The pericardium in this region was removed from the diaphragm and as far around in back as the inferior pulmonary vein. Superiorly it was freed over the auriculoventricular groove, and the auricular appendix of the auricle which was held down in a vise of calcium was finally freed and was seen to retract upwards. A rather large segment of pericardium was removed from the auricular portion as well as the ventricular portion. It was felt at the completion of the operation that a very wide liberation of the left ventricle and left auriculoventricular septal groove had been accomplished. The patient stood the operation well and the color of his blood was normal at its completion although in the beginning he was very cyanotic until the heart had been freed. The lung expanded well. A catheter was left in the space between the heart and the lung in order to provide for evacuation of serum and possibly any air which might result from an undiscovered leak from the lung itself. This was brought out through the center of the incision and is to be removed in 24 hours. The wound was closed in layers by means of interrupted silk sutures with several pericostal sutures of catgut in the intercostal portion of the incision."

The patient's postoperative course was a stormy one through which he was helped by the use of digitalis, quinidine, ammonium chloride, and mercurial diuretics. Throughout his hospital stay the predominant cardiac rhythm was one of auricular flutter. Over a period of 4 to 6 weeks he began to improve as noted by a decrease in respiratory difficulty, a decrease in the size of the liver, and in the amount of peripheral edema, and a decrease in the venous pressure which by the end of February, 1947, had receded from 265 to 190 mm. of water.

Following his discharge from the hospital on March 4, 1947, he remained at home and gradually increased his activities in direct proportion to his general clinical improvement. By the fall of 1947, he was able to walk a long distance without any respiratory embarrassment, to dance, and to increase his minor activities to the maximum. He was easily maintained on digitalis alone and the proof of this reported improvement is mirrored in the fact that his venous pressure in December, 1947, had decreased to 167 mm. of water. Hope for the future seemed bright.

On August 27, 1948, his physician, Dr. M. H. McCaffrey of Pittsburgh, wrote of his excellent health with no evidence whatsoever of congestion of liver, extremi-

ties, neck veins, or lungs. There was still present auricular fibrillation at a well controlled heart rate of 72. He was fully active and able to swim and dance without symptoms.

Comment: Cardiac catheterization has to the present time found much of its clinical usefulness in the diagnosis of congenital malformations, but the adaptability of this procedure as an aid in the localization of the site of constriction has been illustrated in this case and can best be presented graphically: See Fig. 1.) If at Site No. 1 (superior vena cava) the pressure is found to be increased above normal one may suspect constriction around the point of entrance of the great vessels or of the right auricle or right ventricle. This condition would of course prevail in those cases in which there is no important increase in the size of the heart. A pressure increase or even a normal value with a normal pulse pressure at Site No. 2 (right ventricle) would tend to rule out both right ventricular atonia and constriction of the right ventricle, which gives a low pulse pressure in the right ventricle. This would be substantiated by the presence of an increased pulmonary second sound. An increase in the

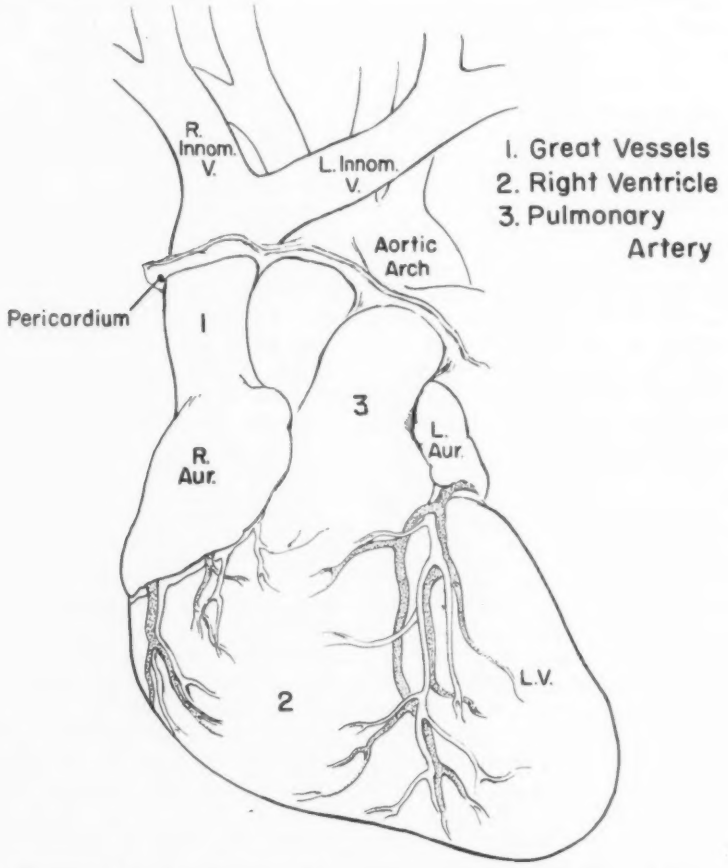

Fig. 1. Diagram of heart to illustrate the positions from which blood was taken by catheter for determination of oxygen content in Case 2.

pressure at Site No. 3 (pulmonary artery) means that the constriction is beyond the right ventricle, presumably in the left heart chambers. Cardiac catheterization is not a formidable procedure and may be of immeasurable aid as a preoperative diagnostic procedure in cases of chronic constrictive pericarditis.

Case 3. R.J., male, aged 20 years, was admitted to the Massachusetts General Hospital on November 17, 1947, because of the onset of dyspnea, syncopal attacks and swelling of the abdomen over a 10 to 12 months period. The patient was rejected for duty in the armed services because of the finding of an enlarged heart by routine Roentgen-ray examination. Because of the continuation of his symptomatology in spite of medical therapy he was referred to this hospital. His family and past history were noncontributory. There was no history of tuberculosis or of any acute infection.

On admission this well developed and well nourished young man was in no acute distress. His neck veins were full. The lung fields were clear. The heart was enlarged to percussion and totally irregular in rhythm at a rate of 72. The heart sounds were of good quality. The blood pressure was 110 systolic, 70 diastolic. There was a double second sound at the base and a third heart sound at the apex, without murmurs. There was no gallop. Of note were the paradoxical pulse, the accentuated pulmonary second sound, and the retraction of the second and third interspaces on the left during systole (Broadbent's sign). The abdomen was prominent and revealed a fluid wave. The liver was enlarged, with edge 3 cm. below the costal margin. The spleen could not be felt nor was there any peripheral edema. The Roentgen-ray film of the heart showed it to be enlarged with considerable prominence of the left auricle and of both ventricles. There were plaques of calcium surrounding the heart incompletely in a circular manner. The electrocardiogram showed auricular flutter-fibrillation with ventricular rate of 90, normal axis, flat T waves in Lead 1, diphasic T waves in Lead CF5, with inversion of all the remaining T waves. This was in keeping with the diagnosis of chronic constrictive pericarditis. The urine and blood were within normal limits. The total protein was 7.35 gm. per 100 gm. with albumin globulin ratio of 1.6. The venous pressure was 270 mm. water. Because of our previous experience of the diagnostic value of cardiac catherization our associate Dr. Gordon Myers carried out the procedure and determined the pulmonary arterial pressure. This proved to be twice its normal value and thus, as in Case 2, indicated the need of decorticating the left ventricle first. In withdrawing the cardiac catheter and taking continuous readings there was no evidence of atonia of the right ventricle or constriction around the great veins.

On December 5, 1947, after the patient had been prepared preoperatively with digitalis and quinidine Dr. Edward Churchhill performed a pericardiectomy by the left transthoracic approach. The incision extended from the midline anteriorly to the midaxillary line over the fifth rib on the left. On exposure the anterior portion of the pericardium seemed relatively free of calcium. A large pericardial calcareous plaque, measuring 3 by 2 cm., over the left auricular appendage and upper portion of the left ventricle was removed. Then the pericardium was removed almost entirely from the left side of the heart posteriorly to the midline Finally the auriculoventricular groove on the left was exposed and the pericardium was almost entirely removed therefrom. Several centimeters of the left side of the diaphragmatic portion of the pericardium were next removed together with a 2 cm. strip of pericardium anteriorly.

The postoperative course was eventful, in that spontaneous diuresis occurred, the patient's weight falling 12 to 14 pounds during the first 11 days after operation. Venous pressure at the end of this time was 185 mm. water. The ventricular rate in the auricular flutter-fibrillation seemed well under digitalis control. Of note was a loud third heart sound at the apex. On December 13, 1947, the patient's satisfactory condition permitted

discharge to his home. There was no remarkable change postoperatively in either the Roentgen-ray shadow of his chest or in the electrocardiogram. The patient was seen 13 days after his discharge and was in the best of spirits and health. He drove his car more than 100 miles just to keep this appointment 3 weeks after his operation and was none the worse for it.

When last examined in the Outpatient Department on July 21, 1948, he was in excellent health, working during the summer and planning to resume school in the autumn. There was no evidence of congestion of neck veins, liver, or lungs. The heart rhythm was irregular at a rate of 80 on daily digitalis therapy.

Comment: This is another case in which the success of our present-day surgery was directly dependent upon the careful preoperative studies, including cardiac catheterization.

Summary. We have herewith reported 3 cases, all male, aged 16, 21, and 20 years respectively, who suffered from chronic constrictive pericarditis involving preponderantly the left heart chambers and who required decortication thereof for relief. The first patient died from the complication of peripheral arterial embolism after two unsuccessful pericardial resections carried out by anterior approach and an omentopexy. The other 2 patients have been greatly benefited, in fact probably cured, as a result of a transthoracic approach allowing free exposure of the side and the back of the heart. The pericardium was removed from the left auricle and left ventricle in these cases. In the first patient, two unsuccessful operations had previously been carried out through the usual anterior approach.

In these 3 patients clinical evidence suggested the correct diagnosis and consisted of accentuation of the pulmonary second sound, cardiac enlargement involving the right ventricle, and a shift of the electrocardiographic axis deviation to the right, with a persistence of chronic congestion. A measurement of the pulmonary blood pressure by cardiac catheterization has been an important test of the left heart chambers in the last 2 cases, confirming by its marked elevation the constriction of the left heart chambers which has acted like mitral stenosis on the pulmonary circulation and right heart.

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CHYLURIA: A REPORT OF TEN CASES

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CHYLURIA is a rare but definite clinentity which has been recognized since Moellenbroccius,[9] in 1670, first designated the condition as chyle in the urine. The writings of Hippocrates, Galen and Theophilus mention fatty and oily urine,[14] and various writers of the Middle Ages described an "excretion of milk," the significance of which was not understood. Wucherer, in 1866, was the first to recognize the relationship between filariasis and chyluria when he demonstrated the presence of microfilaria in the blood and urine of a patient who had chyluria[5]. The physiologic and pathologic studies of Manson, Mackenzie and Block[13] further proved this relationship, and today, chyluria is a well-recognized and fairly common complication of filariasis. Most authors make a sharp distinction between parasitic chyluria, secondary to filariasis or rarely to other parasitic diseases, and nonparasitic chyluria, for the most part of unknown origin.

Carter, in 1862, first suggested the hypothesis of lymphatic obstruction with subsequent abnormal communication between the lymphatic system and the urinary tract (Kutzmann[9]). This undoubtedly occurs in filariasis, in which there is obstruction by a filarial granuloma somewhere between the draining lymphatic ducts of the small intestine and the cephalic end of the thoracic duct. As a result, there is a backflow of chyle into the pelvic lymphatics, from there into a collateral lymphatic system of the abdominal wall, thence into the thoracic duct somewhere above the level of the diaphragm. It is postulated that an incompetency of this collateral system is necessary in order for chyluria to occur. If such an inadequacy exists, back pressure develops in the lymph vessels of the lumbar channels to the kidney, causing rupture of the vessels and subsequent spilling of chyle into the urinary tract. Pathologic studies by Mackenzie and Manson substantiated this hypothesis for the most part (see R. P. Strong)[16]. However, patologic support for this hypothesis when it is applied to nonparasitic chyluria is questionable or lacking. This is in part due to technical difficulty in demonstrating lymph channels in portmortem studies. A secretory hypothesis proposes that the chyle passes directly through the renal epithelium into the urine. This hypothesis is entirely unsupported by objective data. The mechanical hypothesis, then, remains the best explanation to date. Obstruction of the thoracic duct by other lesions, with secondary chyluria, undoubtedly can occur. Posterior thoracic lesions, perirenal abscess, pregnancy, syphilis, tuberculosis and other conditions have all been blamed for the presence of chyluria[15]. However, in few of the cases reported has there

been pathologic proof for the etiologic role of the suspected lesion.

In considering the etiology of chyluria, filariasis should always be kept in mind, even when one is dealing with patients in a temperate climate. A knowledge of the patient's travels is important. The southeastern part of the United States is a filarial endemic region. We suggest also that sporadic filariasis may occur, just as sporadic malaria may occur, in any region where mosquitoes are found. The absence of microfilariae in the blood and urine does not exclude a diagnosis of a previous filarial infection nor of pathologic conditions of filarial origin. A high percentage of persons who have a history of previous filarial infection do not show microfilariae in the blood or urine.

The location of the fistulous opening between the lympathics and the urinary tract may be found anywhere from the kidney to the urethra. In the large majority of instances it is in the pelvis of the kidney.

The incidence of chyluria is, as expected, high in endemic filarial regions. Ray and Rao[13] have reported 254 cases from India. It is of interest to note, however, that whereas filariasis flourishes in some parts of the South Pacific, chyluria in those regions is negligible. More than 100 cases of so-called nonparasitic chyluria in Europe were reported in the literature prior to 1925, according to Kutzmann[9]. Yamauchi[22], in 1945, reviewed data on 45 patients seen by him in Hawaii. In direct contrast, a careful search of the literature from the United States reveals that only 26 cases (including 5 of the 10 reported in this paper) have been recorded since 1916[2–4,6–12,14,17–21]. Twenty of these were designated as being cases of so-called nonparasitic chyluria.

Clinically, the symptoms of chyluria are few. The patient usually complains of passing milky, cloudy or white urine, occasionally containing clots. These clots are coagulated chyle and, if formed in the pelvis of the kidney, the ureter or the bladder, they may cause dysuria. Hematuria is comparatively rare. The milky appearance of the urine is due to a colloidal suspension of fat particles, in distinction to lipuria, in which the fat is in the form of globules visible to the naked eye and stainable with Sudan III. Characteristically, the urine does not clear on centrifugation. Pyelographic studies occasionally show the presence of a pyelolympathic type of backflow[1]. This is not a constant finding of chyluria, and backflow has been reported to be present in the absence of chyluria.

The ages of our patients when they were examined varied from 30 to 64 years. The average age was 47.4 years. The age at the onset of symptoms varied from 19 to 58 years. The average age at onset was 38.3 years. There were four men and six women. Two of our patients lived in Puerto Rico, 1 in British Guiana, 2 in Illinois, 1 in New York, 1 in Arkansas, 2 in Minnesota and 1 in Canada. At least 7 of these 10 either lived in a place where they may have contracted filariasis or had visited places where they could have contracted this infection. Our patients' weights were all normal or greater than normal with the exception of one patient who was slightly underweight. None of our patients had serious symptoms due to chyluria nor was their general health impaired by the chyluria. All passed milky urine; 2 passed chylous clots. The blood of 7 patients and the urine of 5 patients were examined for the presence of microfilariae and in each instance none was found.

Numerous types of therapy have

been employed in the treatment of chyluria, one of the commonest being the instillation of sclerosing solutions into the renal pelvis in an attempt to close the lymphatic fistula. Evaluation of such treatment is difficult, inasmuch as chyluria is characteristically intermittent and recurrent over many years. The use of sclerosing solutions is rarely, if ever, indicated, because the affliction seldom causes the patient any significant distress, and it has been repeatedly proved that the loss of fat and protein in the urine is negligible so far as the nutritional status of the patient is concerned. Arsenical preparations have been employed rather frequently in the tropical countries; but again, as with any type of treatment of chyluria, the results are difficult to evaluate, and in this case, the rationale for such therapy is not understood. Rarely do these patients require any form of specific therapy. It seems to us that there are two conditions which, if present, may need treatment: (1) undernourishment, due to loss of fat through the urinary tract; (2) the presence of fat in the urine in such large quantities that it will precipitate or solidify and form clots prior to excretion. These clots may cause considerable pain and dysuria.

The malnutrition can be controlled by increasing the patient's caloric intake. We believe that one could maintain normal weight and health even though he lost almost all of his fat intake through the urinary tract. This loss could be made up by increasing his carbohydrate and protein intake. The excessive amount of fat in the urine that produces clots can, we believe, be controlled in most instances by reduction of the fat intake, as was shown in case 10, in which, on his

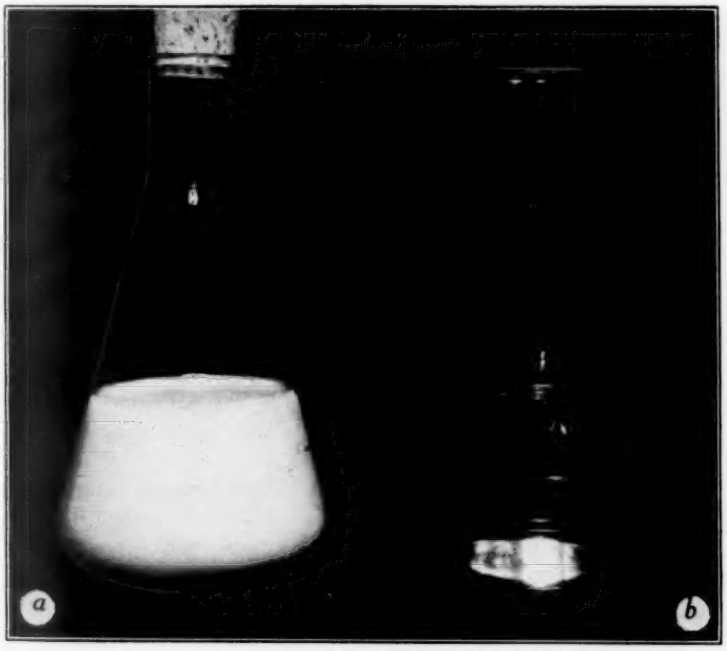

Fig. 1*a*.-A specimen of urine from Case 10. The specimen contained 988 mg. of fat per 100 cc. of urine. *b*. A specimen of normal urine.

usual diet, the patient had 402 mg. of fat per 100 c.c. of urine. On a high fat diet the urine contained 988 mg. per 100 c.c. (Fig. 1) and on a low fat diet it contained only 100 mg. of fat per 100 c.c.

Report of Cases. Case 1. A 47 year old white man was seen at the Mayo Clinic in July, 1932. He complained chiefly of postprandial bloating and belching. Other symptoms of which he complained included insomnia, nervousness and milky urine, the last of which had been present since the age of 21 years. His residence was Arkansas and there was no mention of areas visited by travel except that he had never been outside of the United States. At onset, the milky urine was present daily, particularly in the morning, 2 or 3 hours after breakfast. In more recent years, milky urine had been noted to be present only about once yearly. Physical examination revealed no significant abnormalities except that the patient was underweight. Complete blood count and flocculation reaction for syphilis were normal. The urine was milky in appearance and contained 127.3 mg. of fat and 500 mg. of sugar per 100 cc. Fasting blood sugar and glucose tolerance reactions were normal; however, the urine collected at 30 minute intervals contained sugar and this was regarded indicative of renal glycosuria. Cystoscopic examination and retrograde pyelography were not done. Microfilariae were not found in the blood.

Case 2. A 30 year old white woman, of German-Jewish extraction, was seen at the clinic in August, 1927. Her residence was Illinois and she had traveled in Missouri and Kentucky. Six months prior to her coming to the clinic, sudden severe pain had developed in the right renal region. This pain persisted for 2 hours and spontaneously disappeared with no recurrence. No other symptoms were present but within 1 week she first noted the presence of milky urine. Since onset, the milky urine had been present only in the morning. Physical examination did not reveal any significant abnormalities. Complete blood count was normal. The urine was milky and contained 100 mg. of fat per 100 cc. Erythruria and pyuria were graded 1+ (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition). The value for the total lipoids was 421 mg. per 100 cc. of plasma. The values for blood urea, uric acid, creatinine and serum protein were normal. Microfilariae could not be demonstrated in the blood. Cystoscopic examination did not reveal any point of entrance of chyle into the bladder, and the urine from both ureters was clear.

Case 3. A 58 year old white woman was seen at the clinic on several occasions between 1930 and 1934, at which time the results of general examinations were essentially negative except that they revealed a static type of arthritis. Her residence was Minnesota but she had traveled extensively throughout the southern part of the United States and in Egypt Eight months prior to her last visit to the clinic, the patient had first noted the appearance of milky urine. There were no symptoms referable to the urinary tract. Physical examination did not reveal any significant abnormalities. Complete blood count was normal. The urine contained 25 pus cells per high power field. The values for blood urea and uric acid were normal. On cystoscopic examination, milky urine was seen to spurt from the left ureter and urine collected from the pelvis of the left kidney was milky in appearance and clotted soon after collection. A pyelogram of the left kidney questionably showed backflow. Microfilariae were not present in the urine or blood.

Case 4. A 41 year old woman, a resident of Canada, was seen at the clinic in March, 1935. She complained chiefly of upper lumbar back pain of 4 months' duration. Her past history was not significant and the extent of her travels was not recorded. Milky urine had been present for 1 month. An additional symptom of which she complained was recurrent swelling of the right leg for 4 months. Physical examination did not reveal any significant abnormalities except moderate obesity. Complete blood count was normal. The urine appeared

milky and contained 174 mg. of fat per 100 cc. Albuminuria and pyuria were each graded 1+. The values for blood urea, plasma cholesterol and serum protein were normal. Cystoscopic examination and a left retrograde pyelogram did not reveal any abnormalities.

Case 5. A 64 year old man of Chinese descent, who had been born in California, was at the clinic in 1936. He complained chiefly of passing thick, milky urine. In addition he had occasionally had mild dysuria and the urine clotted on standing. The symptoms had been noted first 7 years prior to his coming to the clinic. They had disappeared spontaneously 2 years later, but recurred 6 months before his examination at the clinic. Physical examination did not reveal any significant abnormalities. The urine was milky and contained 975 mg. of fat per 100 cc. Albuminuria and erythruria were each graded 3+. The plasma values for cholesterol and total lipoids were normal and the blood urea and blood sugar were within normal limits. The blood and urine were negative for microfilariae. On cystoscopic examination, milky urine spurted from the left ureteral orifice, but that from the right was clear. Not only did a retrograde pyelogram of the left kidney reveal pyelolymphatic backflow, but the injected contrast medium was excreted by the right kidney within 5 minutes. A subsequent retrograde pyelogram on the right was normal.

After this procedure, the chyluria did not recur until 6 months before the patient's second visit to the clinic, in 1941. A retrograde pyelogram at that time was negative. Urinalysis revealed milky urine containing 46 mg. of fat per 100 cc. Albuminuria was graded 4+ and erythru- Albuminuria was graded 4+ and erythruria 2+.
2 weeks prior to the patient's next visit, in June, 1946. Examination at that time revealed that the patient had lost some weight, but otherwise there had been no change. A left retrograde pyelogram revealed "marked lymphatic extravasation" medial to the kidney, as was seen originally in 1936.

The patient was last seen at the clinic in August, 1947, when he returned because chyluria had persisted since the previous visit and he now was passing clots, which caused rather severe dysuria. These clots were noted to be numerous in the bladder on cystoscopy. Again, milky urine spurted only from the left ureteral orifice but a left retrograde pyelogram was negative.

Case 6. A 51 year old white man of Spanish extraction, whose residence was Puerto Rico, was examined first at the clinic in 1940, when a diagnosis of recurrent malaria was made. He returned to the clinic in July, 1946, complaining chiefly of aching in the left renal region of 1 year's duration and passage of "thick" urine often containing "chunks" of mucus intermittently for more than 6 years. There was no history obtainable of acute or chronic lymphangitis. Physical examination did not reveal any significant abnormalities other than a rather large right hydrocele. Laboratory examination revealed hemoglobin 14.0 gm. per 100 cc., erythrocytes 4,890,000 and leukocytes 7,400 per cu. mm., with eosinophilia noted on the blood smear. The flocculation reaction for syphilis was negative. A roentgenogram of the thorax was negative. Urinalysis showed a specific gravity which ranged from 1.014 to 1.021; albuminuria, grade 1+ to 3+; erythruria, grade 1+ to 3+; pyuria, grade 1+ (4 to 6 cells per high power field). The urine was milky and reported as "typical of chyluria." It contained 77 mg. of fat per 100 cc. On cystoscopy, a very minute papilloma about 4 mm. in diameter just posterior to the right ureteral orifice was noted and fulgurated. The urine spurting from the ureters seemed clear, but when ureteral specimens were examined, that from the right ureter contained 31 mg. and that from the left 11 mg. of fat per 100 cc. A left retrograde pyelogram revealed rather marked pyelolymphatic backflow.

Case 7. A 45 year old white woman was seen at the clinic in September, 1946. She complained chiefly of symptoms referable to the upper part of the gastrointestinal tract. Her residence was Puerto Rico and she was of Spanish descent. In

addition to the gastro-intestinal symptoms, she complained of the passage of milky urine intermittently since 1940. Urine of this type was passed usually in the first morning specimen, after which the urine was clear during the rest of the day. She gave a history of an acute episode of inguinal lymphadenitis associated with fever and red streaks on the right thigh at 14 years of age, but none since then. Microfilariae had never been demonstrated in the blood. The results of physical examination were negative. Laboratory examination revealed 14.4 gm. of hemoglobin per 100 cc., erythrocytes 4,840,000 and leukocytes 9,400 per cu. mm., with a normal differential count (1% eosinophils). The flocculation reaction for syphilis and a roentgenogram of the thorax were negative. The urine was milky in appearance and its specific gravity was 1.015. Albuminuria and pyuria were graded 1+. Blood and urine were negative for microfilariae.

Case 8. A 49 year old woman was seen at the clinic in February, 1947, having been referred to the clinic for postoperative (panhysterectomy) radium therapy, a diagnosis of carcinoma of the cervix having been made elsewhere. Her residence was British Guiana and it is recorded that she was of British, Spanish and Negro extraction. She complained of the presence of gallstones, which had been known for 5 years, and of the passage of milky urine for 30 years. She stated that she had had a "filarial infection" 30 years previously, but no further symptoms referable to this illness are recorded. Gross hematuria had been present on several occasions as well as the passage of "thick" urine, but there was no history of urinary obstruction. In 1911, a large left inguinal lymph node had been removed, supposedly for filariasis. Physical examination revealed enlarged, firm axillary and inguinal lymph nodes, absent cervix, uterus and adnexa (surgical) and atrophy of the right calf (proved to be secondary to palsy of the right sciatic nerve 16 years previously). Laboratory examination revealed 14.0 gm. of hemoglobin per 100 cc., erythrocytes 4,500,000 and leukocytes 5,700 per cu. mm. The flocculation reaction for syphilis was negative. The urine was milky in appearance. Albuminuria was graded 4+ and erythruria 3+. A roentgenogram of the thorax was negative. A cholecystogram revealed the presence of gallstones. Blood and urine were negative for microfilariae. Examination of cervical tissue (removed elsewhere) by one of the pathologists at the clinic revealed squamous-cell epithelioma, grade 4 (Broders' method). Further investigation of the chyluria was not carried out in view of the necessity for prime attention to the pelvic lesion.

Case 9. A 34 year old white woman was seen at the clinic in July, 1943. She complained chiefly of having passed white urine for 3 months. Her residence was Illinois, but her birthplace and travels were not recorded. In 1937, she had had an episode of urinary obstruction relieved by right ureteral catheterization, the exact cause of the obstruction being undetermined. There had been no symptoms referable to the urinary tract since that time or since she had first noted the presence of milky urine. In 1941, an active pulmonary tuberculous lesion was discovered, for which she was hospitalized from January, 1942 to April, 1943, when the lesion was said to be arrested. Her sputum had been positive for acid-fast organisms. Physical examination did not reveal any significant abnormalities. Laboratory examination revealed 13.1 gm. of hemoglobin per 100 cc., erythrocytes 4,590,000 and leukocytes 4,500 per cu. mm. The specific gravity of the urine was 1.016. Albuminuria was graded 3, erythruria 2 and pyuria 3. The flocculation reaction for syphilis was negative. A roentgenogram of the thorax showed a lesion of the right upper lobe suggestive of tuberculosis. Cultures of urine were negative. No acid-fast organisms were found on examination of the urine or sputum. On cystoscopy, milky urine spurted from the left ureteral orifice and on retrograde pyelography there was suggestive pyelovenous backflow from the tip of the upper calix of the left kidney.

Case 10. A 59 year old white man was seen at the clinic in August, 1947. He complained chiefly of cloudy urine.

The patient was of Spanish-Cuban extraction, born in Key West, Florida. He lived in Florida until the age of 23 years and has lived in Brooklyn, New York, since that time. His only residence outside of the United States was in 1946 for 1 month in Mexico City. His first passage of cloudy urine had been in 1936 and had been accompanied by chills, temperature up to 102° F. and pain and swelling of both knees of 3 to 4 months' duration. No further milky urine was noted until 1946, when there was recurrence of symptoms as before, plus swelling of ankles and all proximal phalangeal joints of hands as well as redness and pain over the "vessels" of both lower legs. The milky urine persisted for 3 to 4 weeks, whereas the other symptoms subsided in 3 to 4 days. The patient was then well until 1 week prior to his examination at the clinic, when there was recurrence of cloudy urine, in which he noted "clots of mucus," and mild arthralgia in knees and hands.

Physical examination revealed bilateral inguinal hernias with an incisional (previous herniorrhaphy) hernia in the left lower quadrant of the abdomen; enlargement of the prostate, grade 2; and moderate pitting edema of both ankles. Laboratory examination revealed 15.6 gm. of hemoglobin per 100 cc., erythrocytes 4,670,000, and leukocytes 5,300 per cu. mm., with 4.5% eosinophils on differential count. The Kline, Kahn, Hinton and Kolmer reactions were negative. The urine was milky in appearance with a specific gravity from 1.017 to 1.025. Albuminuria was graded 4+, erythruria 3+ to 4+ and pyuria 1+ (4 to 20 cells per high power field). A roentgenogram of the thorax revealed torsion of the aorta. The concentration of urea was 30 mg. per 100 cc. of blood, that of uric acid 5.3 mg. per 100 cc. of serum, that of fasting blood sugar 168 and 86 mg. per 100 cc., that of cholesterol 247 mg. per 100 cc. of plasma, that of fatty acids 403 mg. per 100 cc. of plasma, that of total lipoids 650 mg. per 100 cc. of plasma, and that of protein 5.8 gm. per 100 cc. of serum. Serum sulfate, calcium and phosphorus were within normal limits. Blood and urine were negative for microfilariae. On cystoscopy, clear urine was seen to spurt from the right ureteral orifice, and milky urine from the left. The urine contained 402 mg. of fat per 100 cc. on the first examination. After two days of low fat diet, the urine contained 100 mg. of fat per 100 cc. One hour after ingestion of 16 fluid-ounces (473 cc.) of cream, the fat content of the urine was 170 mg. per 100 cc.; after 3 hours, 540 mg. per 100 cc.; after 4 hours, 570 mg. per 100 cc.; after 5 hours, 988 mg. per 100 cc. (Fig. 1).

Summary. We have reported 10 cases of chyluria encountered at the Mayo Clinic. The etiology and pathogenesis of chyluria are discussed. Chyluria is rare, but it is not a widely recognized entity, and should be considered in a differential diagnosis, along with pyuria, phosphaturia and lipuria, whenever a patient complains of milky, cloudy or white urine.

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RELATION OF BODY WEIGHT AND FAMILY HISTORY OF HYPERTENSIVE DISEASE TO BLOOD PRESSURE LEVELS IN UNIVERSITY STUDENTS

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It is generally accepted that overweight is a factor in the production of hypertension. Short and Johnson[6] of the Life Extension Institute compared the blood pressures of 2858 overweight men and 658 men of normal weight whose average age was 40 years. In their series overweight appeared to be a factor in causing an increased incidence of hypertension. This effect was more marked in the diastolic pressures than the systolic.

TABLE 1. MEAN SYSTOLIC BLOOD PRESSURES BY HEIGHT-WEIGHT PER CENT AND AGE—MALE

Age	*Height-Weight %*	*No. Cases*	*Mean Systolic Pressure*	*S.E.*
20 and Under	Under 80%	155	118.7	±.1143
	80–89%	2375	119.5	±.0260
	90–109%	14915	121.7	±.0104
	110–119%	2841	124.1	±.0241
	120% and over	1424	126.7	±.0366
	Total	21710	122.1	
21–30	Under 80%	228	117.2	±.0745
	80–89%	2501	118.9	±.0230
	90–109%	14001	122.0	±.0099
	110–119%	2789	124.0	±.0220
	120% and over	1153	125.6	±.0357
	Total	20672	122.0	
31–40	Under 80%	28	109.5	±.1989
	80–89%	175	117.4	±.0870
	90–109%	717	120.9	±.0442
	110–119%	155	123.1	±.1042
	120% and over	62	123.7	±.1602
	Total	1137	120.6	
41 and Over	Under 80%	10	110.5	±.4050
	80–89%	42	120.7	±.2332
	90–109%	171	123.4	±.1119
	110–119%	41	125.0	±.2010
	120% and over	17	122.7	±.2528
	Total	281	122.8	
All Ages	Under 80%	421	117.1	±.0617
	80–89%	5093	119.1	±.0170
	90–109%	29804	121.8	±.0071
	110–119%	5826	124.0	±.0161
	120% and over	2656	126.1	±.0254
	Total	43800	122.0	

Hartman and Ghrist[4] studied the records of 2042 consecutive patients over 15 years of age at the Mayo Clinic. In about an equal number of men and women they found a consistent rise in the mean systolic blood pressures with an increase in weight. The mean diastolic pressures were found to increase with weight in women only. Alvarez,[1] Gager,[3] Symonds[6] and others have also reported studies showing this same general relationship between overweight and blood pressure.

In an earlier paper[2] the relation between age and mean blood pressure levels for 43,800 men and 31,458 women was reported by us. The group was composed largely of University students with an average age of 21 years. The blood pressure readings of this same group of over 75,000 students have been correlated with height-weight % to determine what relationship there may be in young adults between body weight and blood pressure levels.

The height-weight % for each person in the group was computed according to the Medico-Actuarial tables. In the following discussion, the term weight is used to designate the height-weight % rather than actual body weight. Five weight groups were selected, the lowest including those persons falling below 80% of the standard, and the highest those 120% or more of the standard. In this same group of individuals,[2] it had been shown that in women the mean systolic blood pressure increased with age. In order to minimize the age factor in determining the effect of weight on

TABLE 2. MEAN SYSTOLIC BLOOD PRESSURES BY HEIGHT-WEIGHT PER CENT AND AGE—FEMALE

Age	*Height-Weight %*	*No. Cases*	*Mean Systolic Pressure*	*S.E.*
20 and Under	Under 80%	362	107.6	±.0684
	80–89%	3383	107.8	±.0209
	90–109%	12106	109.1	±.0110
	110–119%	1862	111.6	±.0284
	120% and over	1086	115.0	±.0397
	Total	18799	109.4	
21–30	Under 80%	367	111.0	±.0570
	80–89%	2571	111.3	±.0214
	90–109%	6610	112.9	±.0135
	110–119%	939	114.2	±.0363
	120% and over	542	117.5	±.0531
	Total	11029	112.8	
31–40	Under 80%	83	113.4	±.1599
	80–89%	315	114.8	±.0738
	90–109%	699	115.9	±.0469
	110–119%	80	118.4	±.1364
	120% and over	85	121.1	±.1557
	Total	1262	116.0	
41 and Over	Under 80%	18	128.4	±.4657
	80–89%	77	121.0	±.1577
	90–109%	206	124.2	±.1264
	110–119%	37	127.5	±.3285
	120% and over	30	138.8	±.4869
	Total	368	125.3	
All Ages	Under 80%	830	110.1	±.0450
	80–89%	6346	109.7	±.0150
	90–109%	19621	110.8	±.0086
	110–119%	2918	112.8	±.0227
	120% and over	1743	116.5	±.0328
	Total	31458	111.0	

blood pressure, 4 age groups were established. The mean systolic blood pressure of each of the 5 weight groups within each of the 4 age groups was computed (Table 1).

In men the mean systolic blood pressures increase as the weight increases in every age group except in the group 41 and over where the number of cases is small. These increases are statistically significant. The same trend in mean systolic blood pressures with increase in weight was found in women with the exception again in the small group over 40 years of age (Table 2). When all ages are combined this same general trend is evident.

There is not the same definite relationship between the weight and the mean diastolic pressures as that seen in the systolic pressures. In men in the ages between 21 and 40 there is a significant increase in mean diastolic pressure with increasing weight. This is not found in the group under 20 years of age or that over 40 (Table 3). In women there is even less correlation between the diastolic pressures and weight. The only age group showing significant differences in the diastolic pressures and weight increase is the 31 to 40 years (Table 4). Short and Johnson[5] found a similar increase in the mean diastolic pressures with increase in weight in men. Hartman and Ghrist,[4] however, in their series found no correlation between weight and the mean diastolic pressures in men but did find an increase in the diastolic pressures with increased weight in women.

In order to determine the relative effects of age and weight on both sys-

TABLE 3. MEAN DIASTOLIC BLOOD PRESSURES BY HEIGHT-WEIGHT PER CENT AND AGE—MALE

Age	*Height-Weight %*	*No. Cases*	*Mean Systolic Pressure*	*S.E.*
20 and Under	Under 80%	155	73.9	±.9837
	80–89%	2375	72.7	±.2209
	90–109%	14915	72.6	±.0906
	110–119%	2841	73.7	±.2083
	120% and over	1424	75.2	±.2973
	Total	21710	72.9	±.0748
21–30	Under 80%	228	74.2	±.6589
	80–89%	2501	74.9	±.1926
	90–109%	14001	76.0	±.0831
	110–119%	2789	77.5	±.1871
	120% and over	1153	79.7	±.3002
	Total	20672	76.3	±.0686
31–40	Under 80%	28	72.0	±1.3000
	80–89%	175	75.8	±.7256
	90–109%	717	78.3	±.3493
	110–119%	155	80.5	±.7774
	120% and over	62	81.0	±.9151
	Total	1137	78.2	±.2800
41 and Over	Under 80%	10	77.5	±3.1781
	80–89%	42	80.0	±1.5504
	90–109%	171	81.6	±.8258
	110–119%	41	84.0	±1.5407
	120% and over	17	81.6	±2.3181
	Total	281	81.5	±.6290
All Ages	Under 80%	421	74.0	±.5225
	80–89%	5093	74.0	±.1435
	90–109%	29804	74.6	±.0616
	110–119%	5286	75.7	±.1404
	120% and over	2656	77.3	±.2121
	Total	43800	74.7	±.0510

tolic and diastolic pressures, the mean pressures for each weight group by ages is shown graphically in Figure 1. In men under 40 years of age, increased weight is associated with a higher mean systolic pressure, although in no weight group does age seem to influence the systolic pressure levels except after 41 years of age. In women, however, both increased weight and age are factors in producing higher systolic pressures.

There is an upward trend in the mean diastolic pressures of both men and women for each height-weight group as the age increases. This is more marked in women than in men (Fig. 1).

Information was available in the health records of these students regarding a family history of hypertension and cerebral hemorrhage. It seemed of interest to determine whether there were any differences in the mean systolic pressures of those individuals with a history of hypertension or cerebral hemorrhage in their families and in those with no such history. These data are presented in Tables 5 and 6. The mean systolic pressure in both men and women in those with no family history of hypertensive disease is lower than those with such a history. While these differences are statistically significant, they are not very striking. Even in those individuals in whose families instances of both hypertension and cerebral hemorrhage had occurred, the mean systolic pressures were little different.

TABLE 4. MEAN DIASTOLIC BLOOD PRESSURES BY HEIGHT-WEIGHT PER CENT AND AGE—FEMALE

Age	*Height-Weight %*	*No. Cases*	*Mean Systolic Pressure*	*S.E.*
20 and Under	Under 80%	362	67.6	± .5843
	80–89%	3383	67.0	± .1903
	90–109%	12106	67.7	± .0996
	110–119%	1862	68.9	± .2536
	120% and over	1086	71.0	± .3461
	Total	18799	67.9	± .0806
21–30	Under 80%	367	71.9	± .4968
	80–89%	2571	71.4	± .1934
	90–109%	6610	72.1	± .1187
	110–119%	939	73.4	± .3178
	120% and over	542	75.3	± .4310
	Total	11029	72.2	± .0927
31–40	Under 80%	83	72.8	±1.1782
	80–89%	315	74.5	± .3326
	90–109%	699	75.4	± .3746
	110–119%	80	77.6	±1.1937
	120% and over	85	78.4	±1.1658
	Total	1262	75.3	± .2879
41 and Over	Under 80%	18	83.9	±2.8839
	80–89%	77	76.8	±1.1156
	90–109%	206	79.2	± .9772
	110–119%	37	80.7	±1.8470
	120% and over	30	87.2	±2.9414
	Total	368	79.7	± .6970
All Ages	Under 80%	830	70.4	± .3766
	80–89%	6346	69.3	± .1360
	90–109%	19621	69.6	± .0775
	110–119%	2918	70.8	± .2015
	120% and over	1743	73.0	± .8682
	Total	31458	69.8	± .0616

Summary. 1. The relation of body weight and family history of hypertensive disease to blood pressure levels in 75,258 students examined at the University of Minnesota has been studied.

2. In both men and women, the mean systolic blood pressures were found to rise as the weight increased in each age group through 40 years of age.

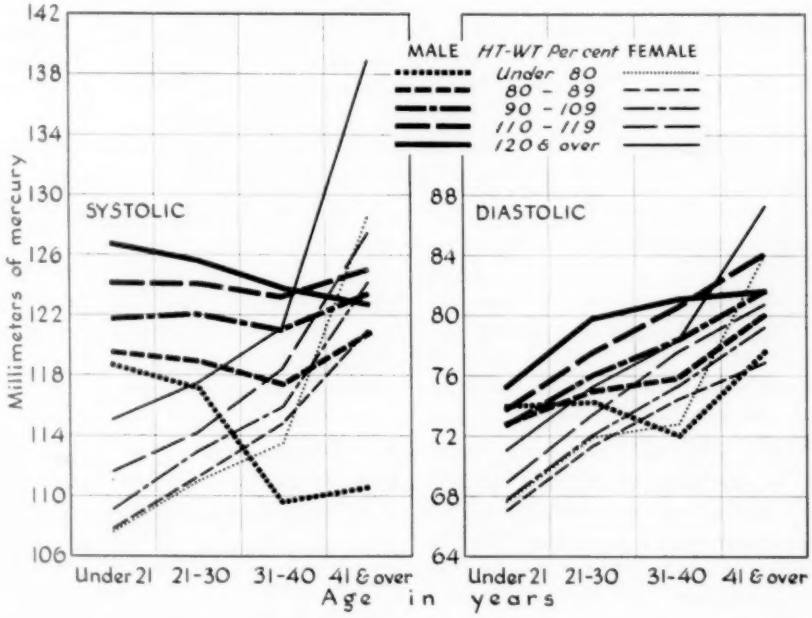

FIG. 1.—Mean systolic and diastolic blood pressure for 5 weight groups by age

TABLE 5. MEAN SYSTOLIC BLOOD PRESSURES ACCORDING TO FAMILY HISTORY OF HYPERTENSIVE DISEASE—MALE

Family History of	*Number of Cases*	*Mean Pressure*	*Standard Error*
Cerebral hemorrhage	6985	122.2	± .1483
Hypertension	10559	122.8	± .1208
Cerebral hemorrhage and hypertension	2781	122.6	± .2317
Neither	29037	121.8	± .0728

TABLE 6. MEAN SYSTOLIC BLOOD PRESSURES ACCORDING TO FAMILY HISTORY OF HYPERTENSIVE DISEASE—FEMALE

Family History of	*Number of Cases*	*Mean Pressure*	*Standard Error*
Cerebral hemorrhage	6609	111.7	± .1523
Hypertension	8601	111.6	± .1342
Cerebral hemorrhage and hypertension	2814	112.3	± .2347
Neither	19062	110.7	± .0883

TABLE 7. MEAN SYSTOLIC BLOOD PRESSURES IN PERSONS WITH ABNORMALITIES OF CARDIAC STRUCTURE OR FUNCTION—MALE

Persons with	*No. of Cases*	*Mean Pressure*	*Standard Error*
Congenital cardiac defect, valvular defect, or cardiac hypertrophy	291	129.9	± .9831
Tachycardia only	1637	128.6	± .3685
No evidence of cardiac abnormality	41872	121.7	± .0592
Total	43800	122.0	± .0592

TABLE 8. MEAN SYSTOLIC BLOOD PRESSURES IN PERSONS WITH ABNORMALITIES OF CARDIAC STRUCTURE OR FUNCTION—FEMALE

Persons with	*No. of Cases*	*Mean Pressure*	*Standard Error*
Congenital cardiac defect, valvular defect, or cardiac hypertrophy	207	117.2	±1.1663
Tachycardia only	1777	116.8	± .3265
No evidence of cardiac abnormality	29474	110.7	± .0700
Total	31458	111.0	± .0693

3. There was less effect of overweight on the mean diastolic pressures. In men in the age groups between 21 and 40 there was a significant rise in the mean diastolic pressures as the weight increased. In women, this relationship was seen only in the 31 to 40 age group.

4. In men up to 40 years of age, overweight rather than age seemed to be an important factor in producing higher systolic pressures, while in women, both weight and age seemed to exert an influence on systolic pressure levels.

5. A family history of hypertensive disease was associated with slightly higher mean systolic pressures in both men and women.

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THE CONTROL OF CIRCULATORY STASIS BY THE ELECTRICAL STIMULATION OF LARGE MUSCLE GROUPS

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THERE is little need these days to remind readers of the value of early movement after operation as a preventive of venous thrombosis and pulmonary infarction. Many patients however fear or resent the attendant discomfort. In others, unconsciousness, weakness or senility may exclude active movement. In all of these cases passive movement might supply the answer, but passive movement and massage on a large scale in a big hospital with many surgical operations is expensive. Any other procedure that ensures movement of venous blood without discomfort should therefore be a welcome addition to post-operative treatment, not only to prevent venous thrombosis, but to avoid peripheral circulatory failure.

The physiological considerations involved are briefly as follows: Circulation is maintained by three sets of pumps strategically placed along the blood circuit, viz. the heart, the voluntary muscles and the diaphragm. One of the essentials for efficient cardiac activity is a mechanism for returning an adequate volume of venous blood to the heart. This is maintained by skeleton muscle contractions (muscle pump) and by the piston-like action of the diaphragm during respiration (respiratory pump). Increased muscular activity therefore automatically tends to increase cardiac inflow and output.

The various causes of circulatory failure include loss of blood volume, failure of cardiac, muscle or respiratory pumps and the loss of vascular tonus. Although a vast amount has been written concerning most of these, it is only in recent years that we have begun to appreciate the role of the muscle pump, particularly as regards stagnation of blood in the lower limbs and the relation of this condition to post-operative shock and thrombosis with pulmonary embolism.

Some years ago it occurred to us that such stasis might be overcome by the artificial induction of muscle activity, for instance, by rhythmical electrical stimulation.

Since thrombi form most often in the legs, especially in the veins of the calf muscles, and leg muscles are the most readily accessible for electrical stimulation, we decided to confine our work to this area. Preliminary observations, herein reported, were made on that form of peripheral circulatory stasis and failure which is so readily induced by the force of gravity in certain subjects when suspended or lying immobile at an angle of 70 degrees from the horizontal (gravity shock or orthostatic circulatory insufficiency). The evidences of this state are an increase of heart rate and diastolic pressure, a decrease of pulse pressure and systolic pressure, together with some pallor, sweating and distress. The application

of the method to the treatment of traumatic shock and the prevention of post-operative thrombosis in this hospital will be recorded on another occasion. Our results so far are distinctly encouraging.

Methods. 1. *Production of stasis.* Circulatory stasis in the lower extremities was produced by the technique of "gravity shock" caused by the passive maintenance of a 70° angle from the horizontal by a subject on a tiltboard. The subjects had previously been found sensitive to this procedure and trained for complete relaxation and immobility.

2. *Source and type of electric current.* Passive muscular contractions in the thigh and calf were induced by a sinusoidal current (surging interrupted direct current with alternating polarity) from a Burdick Morse Wave generator M-210 at an intensity and frequency comfortable to the individual subject. This was usually at 20 to 30 milliamperes intensity and at a rate of 18 to 20 contractions per minute.

3. *Electrodes.* In the early experiments, the dispersive electrode, applied to the lumbo-sacral region, consisted of a thick stockinette girdle soaked in warm saline with a Crooke's metal contact. This was covered with rubber sheeting and held in place by a many-tailed surgical binder. The active electrodes were spiral muslin binders of fourfold thickness applied damp and as warm as tolerated from the ankle to groin. Half-inch ribbons of Crooke's metal were spiraled the full length of the binders and the whole covered with oiled silk held in place with ace bandages.

In later experiments, the dispersive electrode consisted of a thick square Burdick electrode pad 10 x 10 inches, thoroughly moistened with warm normal saline and held firmly in place over the lumbo-sacral region with a many-tailed binder. The active electrodes were similar rectangular pads, 3 x 12 inches each, applied to the dorsal surface of the calves and held with binders of dental dam rubber. Bifurcated and single leads connected the active and dispersive electrodes respectively to the generator.

4. *Procedures.* Pulse rates were determined at the radial artery on one arm and blood pressures (with a mercury or an aeroid manometer) on the other arm at one minute intervals. Circulation times were determined by the sodium dehydrocholate method. Since ankle to tongue time determinations were obviously impractical, antecubital to tongue determinations were made on the assumption that if our experimental procedures resulted in significant changes in the blood pressure of the radial artery, these changes would be reflected in similar variations in circulation time in the arm. In order to demonstrate any alterations in the velocity of venous return, the circulation time of the subject during gravity shock was compared with that of the same subject under the influence of muscle stimulation in otherwise identical circumstances.

Experimental observations. The subjects were healthy adults from 23 to 58 years of age. Thirty-two experiments were made.

All experiments were preceded by a 30 minute stabilization period, with the subject lying horizontal on the tilt-board in a warm, quiet and darkened room. After 10 minutes of basal observations, the subject was passively tilted to a 70° angle and maintained in that position during the period of observations.

1. *Controls* (i.e. not receiving electrical stimulation) were held at the critical angle until symptoms of gravity shock occurred. These usually became manifest when the pulse pressure had dropped to ⅓ or ¼ of the basal level. The time varied from 10 to 50 minutes. Return to the horizontal position brought about prompt and complete recovery. Fig. 1 shows a typical gravity shock reaction.

2. *Intermittent Electrical Stimulation.* In these cases, gravity shock symptoms were allowed to develop before the introduction of muscular contractions by electrical stimulation. Bouts of alternating stimulation and

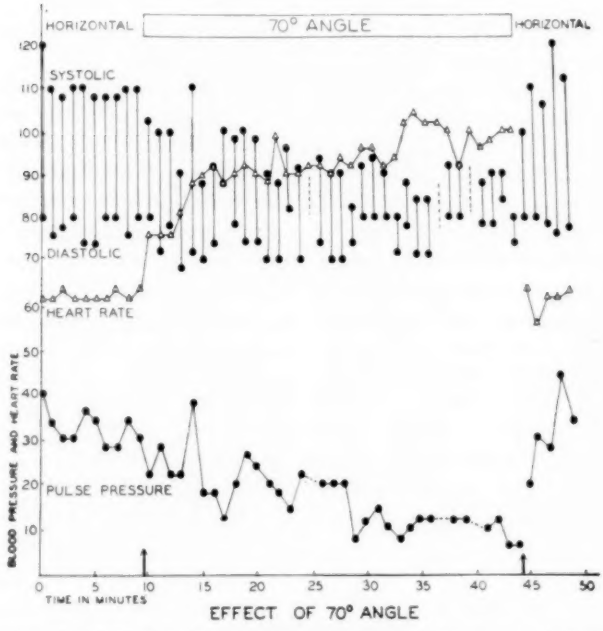

Fig. 1.—Showing the fall of pulse pressure and rise of heart rate induced by gravity in certain subjects when immobilized at an angle of 70° from the horizontal (gravity shock).

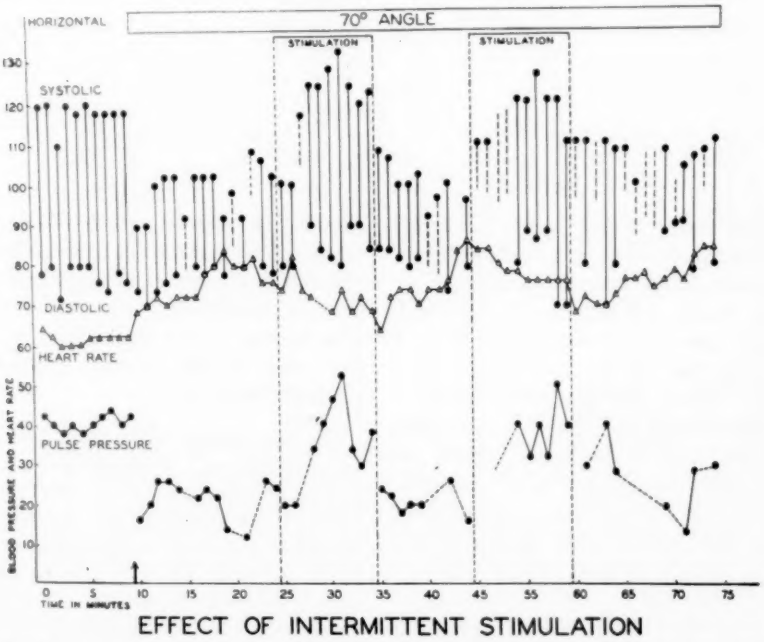

Fig. 2.—Showing the alterations in pulse pressure and heart rate in gravity shock and their restoration to normal during 2 periods of rhythmical muscle stimulation.

rest caused corresponding periods of recovery and relapse (Fig. 2).

3. *Continuous Electrical stimulation.* When electrical stimulation with accompanying contractions was instituted before tilting to the 70° angle and continued for the duration of the experiment, no signs of gravity shock developed.

4. *The circulation time*, determined during the period of circulatory stasis immediately preceding the "blackout" of gravity shock, was abnormally prolonged in all subjects. When however the experiments were repeated under identical circumstances, except that rhythmical muscle stimulation was maintained throughout, the circulation times were shortened to within normal limits (Table I).

changes in circulation time from antecubital fossa to tongue, as illustrated in four subjects.

Objection might of course be made that the reversal of the signs of gravity shock might be the result of emotional disturbances consequent to the mild discomfort of the electrical treatment. When however the type of current employed was one that produced similar discomfort without motor response, the course of gravity shock was unaffected.

Conclusions. A simple method of aborting or preventing the peripheral circulatory failure of gravity shock has been described.

The method is now being applied in this hospital: (a) in the treatment of traumatic shock, and (b) as a preventive of post-operative shock, venous stasis and thrombosis. To date, some 60 patients have been treated, but these numbers are too small to warrant conclusions. It is hoped, however, that the method will be tried and reported in other hospitals.

TABLE 1.

Circulation Times (antecubital fossa to tongue)

Subject	In gravity shock at 70°	During electrical stimulation at 70°
F.L.A.	24 sec.	16 sec. (right arm)
	15	7 (left arm)
M.K.C.	27	16
	27	14
E.N.D.	41	28
B.J.	30 plus	28

Discussion. Rhythmical electrical stimulation, applied to the muscles of the lower extremities of a subject in gravity shock, not only arrests the fall of pulse pressure and acceleration of heart rate, but rapidly restores them to normal. When the stimulation was introduced before the patient was subjected to the hydrostatic effects of gravity, the symptoms and signs of gravity shock are prevented completely.

That the peripheral circulation is retarded during gravity shock, and restored to normal by electrical stimulation, is shown by the corresponding

We are greatly indebted to the Burdick Corporation of Milton, Wis. for their generous gifts of a M-210 generator (now replaced by small portable model) and for technical help and advice, and to Dr. F. A. Hellebrandt, chief of the Baruch Center of Physical Medicine, for her active cooperation in all phases of the work.

* This subject had to be returned to the horizontal position before the end-point was reached.

ANTHRAX: 36 HUMAN CASES OF THE EXTERNAL TYPE TREATED SUCCESSFULLY WITH PENICILLIN

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Human anthrax is a disease for which no active prophylaxis has yet been developed. The prevention of this disease is, for the most part, dependent upon the control of the infection in animals and the employment of general hygienic and sanitary measures. As the disease in humans is contracted through the handling of infected animals and their products, it is seen principally as an occupational disease in veterinarians and workers in wool and leather industries. Reports of the Philadelphia Health Department indicate that the incidence of anthrax in this city shows no tendency to decrease. In the period from 1904-1947 there were reported to the Philadelphia Health Department 433 cases with 50 deaths, a mortality of 11.5%. The source of contact in these cases was traced to imported hides, skins, wool, hair or their products[3]. In 5 patients, a store owner, the wife of a hide dealer, a machinist, and 2 unemployed persons, the source of infection could not be discovered.

Great advances have been made in the treatment of this disease since the use of specific antiserum was reported by Marchoux in 1895 and by Sclavo in 1903. Bacteriophage was employed by Villega Ruiz[5], and Pijper[4] in 1926 reported the use of neoarsphenamine for the treatment of anthrax.

The present study deals with a series of 36 consecutive patients who were treated with penicillin alone. The first 3 cases of this series were reported in a preliminary report in 1944[2]. The first patient was treated on 11-1-43, and the last on 12-23-47.

Distribution of Patients According to Source of Infection

Wool	25
Goat Skin	4
Hides	3
Goat Hair	2
Horse Hair	2
	36

The preponderance of infections in wool workers is apparent from the above table. The wool handlers include twisters, blenders, carpet yarn reelers, carpet burlers, spinners, winders, sorters, combers, and pickers. Other patients worked as trucker, hair doffer, machinist, shipper, stripper, and glazer.

Location of Lesion

Arm—lower arm	19	
upper arm	2	21
Face		10
Neck		2
Shoulder		1
Chest		1
Back		1
		36

The exposed parts of the body were most frequently affected. It is presumed that all cases, which were of the cutaneous type, were contracted by direct contact with contaminated material. In many instances the organism was probably inoculated into the skin or hair follicles by repeated irritation. Lesions on the forearm were more common in yarn twisters who carried skeins of yarn over the arm and in

spinners who carried the spools by the armload.

Twenty-one patients were males and 15 were females. There was no preference for sex except as the occupation was influenced by the requirement of special skills peculiar to the sex.

Because the disease is an occupational one, the patients are for the most part in the older age group, and age of the patient has otherwise no bearing on the incidence of the disease. The youngest was 18 years old; the oldest, 75 years. Social and economic factors as they affected employment over this period were factors which strongly influenced the distribution of patients by sex as well as by age.

The yearly distribution of cases was as follows: 1943–3 (Nov.-Dec.); 1944–2; 1945–7; 1946–14; 1947–10.

A definite history of trauma was obtained in 3 cases. One patient who developed a lesion on the shoulder was a trucker who carried hides, another patient developed a lesion on the tip of the nose where oil drippings had traumatized the skin, and the third patient, the only one in this group with a multiple lesion, was struck with a block on the forehead where the anthrax infection later appeared.

Duration of Disease at Time of Admission to Hospital

Days	No. of Patients
1	3
2	5
3	10
4	7
5	5
6	3
9	2
15	1

The average duration of disease was 4 days before patients were admitted to the hospital. The average stay in the hospital was 14 days, the range was from 7 to 36 days.

Bacteriology: The discharge from the lesion was placed on a slide for examination and plain blood agar culture tubes were inoculated, immediately on admission, then once daily until 2 successive negative smears and cultures were obtained. A blood culture was taken on each patient immediately upon admission.

Results of Smears and Cultures

Smear	Culture	%
Positive	Positive	52.7
Negative	Positive	19.4
Positive	Negative	11.1
Negative	Negative	16.6

Thus bacteriologic confirmation of the diagnosis was possible in 83.4% of the cases, and in the majority of the cases both smears and cultures were positive for anthrax bacillus. In the 6 cases (16.6%), where the diagnosis was not confirmed bacteriologically, the characteristic appearance of the lesion left no doubt as to the clinical diagnosis.

Days of Penicillin Treatment Necessary to Render Cutaneous Anthrax Lesions Bacteriologically Negative

Days of Penicillin Treatment	No. of Patients
1	9
2	9
3	9
4	1
5	1
6	0
7	1

Of the bacteriologically positive cases, 30% became negative 24 hours after treatment was instituted. The same number became negative after 48 hours and an equal number after 72 hours, so that a total of 90% of the cases had become negative after 72 hours of penicillin therapy. One patient who had negative smears and cultures for 6 days had a positive smear on the 7th day. Another patient who received 6 injections of sodium penicillin (total 150,000 units) before admission had negative smears and cultures on each examination, while

another patient who was treated with oral penicillin had positive smear and culture from the lesion when admitted to the hospital on the 15th day of disease. Blood culture in each case was reported sterile.

TREATMENT: The dictum of "hands off" was strictly followed. Except to obtain vesicular fluid for bacteriologic study, the lesions were not disturbed. A plain sterile dressing was used to cover the lesion, sometimes a bland ointment was used to prevent adhesion of the dressing. When possible, loose bandages or binders were used in preference to adhesive tape to secure the dressings. Because of the absence of pain it was difficult to rely on the patient voluntarily to immobilize the part involved. It was occasionally necessary to splint an extremity in order to discourage excessive motion.

Because of the absence of pain in this disease, it is rarely necessary to administer narcotics or analgesics. The location of the lesion in certain parts of the body where the subcutaneous tissue is sparse may cause considerable discomfort but never enough to be a serious problem. Edema is present in every case in a varying degree. When edema is in or near a vital structure such as the eye or neck, it may require urgent and concerted effort to abate it. In such instances it is easier to inhibit edema by the early and continuous application of cold to the part.

The only specific treatment employed in the group being reported was sodium penicillin solution. Except for the first 3 patients who received penicillin intravenously, penicillin was administered intramuscularly. The majority of the patients in this group were given between 100,000 to 200,000 units in a 24-hour period at 3 hourly intervals.

In most cases the lesions were regressing after the smears and cultures became negative on 2 successive days, at which time treatment was discontinued. The first 3 cases of anthrax in this group apparently responded satisfactorily to doses which were much smaller than were used subsequently. The earlier cases received from 50,000 to 100,000 units in 24-hour period.

Comment: It was observed that in many cases, the lesions continued to spread and the edema increased for 24 to 36 hours even after treatment was begun. In the past when patients were treated with antiserum, this phenomenon was frequently observed. It was postulated that a reaction between the infection and the specific serum occurred which was manifested as an inflammatory reaction. It may be that such may also be the case when penicillin is employed. Another hypothesis which may explain the reaction is that the infective process is accelerated by the specific therapy so that the anthrax lesion proceeds along a definite pattern which eventually terminates in resolution of the lesion. The presence of a "tissue damaging factor" has been considered by some, so that the infection may progress to a fatal termination even though the cultures from the blood and lesion are sterile[1].

It was not necessary to use adjunctive treatment for the patients herein reported. Specific anti-anthrax serum is not available commercially at the present time, but we contemplated the transfusion of any patient who did not respond to penicillin with immune whole blood which might be available from persons who have recently recovered from anthrax.

There were no untoward reactions to penicillin in our cases which warranted the cessation of its administration.

Conclusions and Summary: Thirty-six patients with uncomplicated cutaneous anthrax were treated with sodium

penicillin in doses from 100,000 to 200,000 units daily.

The cutaneous lesions became negative in 27 of 30 bacteriologically positive cases after 3 days of penicillin treatment.

Penicillin apparently has no direct or immediate effect on the tissue damaging factor of cutaneous anthrax.

Intramuscular penicillin may be safely used successfully to treat cutaneous anthrax.

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AN EPIDEMIC OF TULAREMIA TRANSMITTED BY INSECTS IN SETTLEMENTS OF DEPORTATION, ASINO AND JAJA, SIBERIA, SOVIET RUSSIA: REPORT OF 121 CASES.

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The knowledge of those forms of tularemia which are not common in America contributes to a better understanding of this disease. While a political deportee, the author had the opportunity to observe an uncommon and interesting epidemic outbreak of tularemia in Siberia, USSR. The data accumulated warrant publication, since no similar observation could be found in the American literature.

Tularemia is an American disease. It was first described here in rodents by McCoy and Chapin[12,13], who also discovered the *Bacillus Tularense*. Other early contributions to this subject also came from the United States; Wherry[28] reported the transmissibility of this disease to man, Francis[5,6] gave the classical description of this condition as it occurs in man and named it tularemia, Foshay[2] developed the diagnostic allergic reaction and introduced serum treatment for this disease. Subsequently tularemia was recognized in many other countries but the two most important reservoirs of this disease are still the United States and Soviet Russia.

There are great differences in the epidemiology and the clinical picture of tularemia in these countries. This becomes clear when the American literature [2,3,5,6,9,11,12,13,22,23,27,28] is compared with the Russian reports on the subject.[1,8,10,15,21,24,25,26,29]

The main animal reservoir of tularemia in the United States is composed of ground squirrels, cotton-tail rabbits, snow-shoe hares, and many other rodents. On the other hand the main source of infection in Soviet Russia consists of water-rats (*Arvicola amphibius*) and to smaller extent of ground-rats (*Arvicola terrestris*), musk-rats and meadow-mice (*Microtus*), while rabbits, squirrels and hares play a far lesser role.

According to Foshay[4] more than 90% of human cases in the United States result from direct contact with infected rodents and their tissues, fluids and pelts. Since the seasonal distribution of tularemia in the United States depends on this factor, outbreaks of the disease occur from April to October when jack-rabbits are handled, November to January when cotton-tail rabbits are hunted, March to September when the disease is transmitted from rodents by ticks, and June to September, if the vector is *Chrysops Discalis* (Meyer[14]). In Soviet Russia the seasons of tularemia are as follows: April to June if the epidemic is due to rats; at this season the infected water-rats start to populate shores of the rivers after floods have subsided and are hunted by rat-hunters; late fall and winter, if the epidemic is epizootic among meadow-mice, which infect the grain placed in stacks; summer, if the epidemic is due to

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transmission of tularemia by insect vectors.

The main vectors of tularemia in the United States are the following insects: the deer-fly (*Chrysops discalis*), stable fly (*Stomoxis calcitrans*) and wood- or dog-ticks (*Dermacentor andersoni* and *Dermacentor variabilis*). In Soviet Russia the following insects (besides those enumerated above) are considered capable of transmitting tularemia: mosquitoes (*Anopheles maculipennis, Culex apicalis, Aedes caspius*, and others), midges (*Chironimidae*) and small flies (Buffalo-gnats, *Simulia*).[21]

There are some distinct differences also in the clinical picture and mortality of tularemia in the United States and in Soviet Russia:

The chief type in both countries is the ulcero-glandular. While in the United States more than 90% of lesions are located on the upper extremity, in Russia only 65 to 70% of the cases show this localisation. The ocular form is much more frequent in the United States than in Russia. On the other hand the anginous form, which has been describmany times in Soviet Russia, is practically unknown in the United States.

The pulmonary complications of tularemia are extremely rare in Soviet Russia but are very common in the United States. Because of the virulence of the American strain of *B. tularense* and its affinity for the respiratory tract, the mortality in the United States was much higher than in Russia prior to the advent of streptomycin. According to the United States Public Health Service the American mortality rate was 5.6%. In Soviet Russia the mortality rate was approximately 1.0%.

Epidemic outbreak of tularemia in Asino and Jaja, Siberia. The settlements of deportation Asino and Jaja are situated in the province of Novosibirsk in the South Eastern corner of the great Western-Siberian Plain approximately at the 85th degree of Eastern longitude and 58th degree of the Northern latitude. Asino lies about 100 miles to the North of Tomsk and forms the terminus of a railway branch running from this town to the North. Asino and neighbouring Jaja are situated within "tajga", that is, dense, low, leafy and coniferous woods. The settlements are surrounded with moors and swamps and lie at the Czulym river, which belongs to the basin of the great river Ob.

The basin of the river Ob has been known as a tularemic area since 1930, and scattered cases of tularemia have been noted among water-rat hunters and the native population working with rat-pelts. The water-rats are encountered in large amounts on the shores of the river Czulym and adjacent stagnant waters. Moreover, a few meadow-mice and field-mice as well as some hares and squirrels are encountered near inhabited places. Swarms of insects are found in this region. The meadows and woods are crowded with mosquitoes (*Culex, Aedes* and *Anopheles* varieties) as well as with *Simulia* and midges. Swarms of flies (*Musca domestica* and *Stomoxis calcitrans*) are found in close proximity to inhabited barracks and live-stock. *Chrysops discalis* is encountered infrequently on the shores of rivers and marshes; ticks are found only in the woods.

The average winter temperature is between -20° and -40°C. The average summer temperature in July is between 10° and 20°C. The summer of 1941 was, however, warmer than usual.

At that time the population of the settlement Asino was composed of 1840 Polish citizens, who in June, 1940, were forcibly deported to Siberia from Eastern Poland occupied by Russians at the outbreak of the World War II. The population of the adjacent settlement of Jaja, located only a few miles from Asino, consisted of 460 peasants deported from Poland at the same time,

and mostly of Ukrainian nationality. The population of other adjacent villages (Asino, Woronopasche, Feotistowka, Trichomirowka, Wozniesiensko, Kalinowka, Nowikowka, Puszkino, Ilinskij, Tuistat, and others) consisted only of Russian peasants, most of whom had been transferred and deported to Siberia from the Russian Ukraine in the pre-war years.

The hospital of the settlement Asino was located in wooden barracks of the settlement Sosnowka, and belonged previously to one of the jail settlements of the "Tomasinlag" *. It had a capacity of about 100 beds and took care of the entire Polish population of the settlements Asino and Jaja, as well as the Russian population of all the adjacent villages. The hospital had an out-patient department which was run by 6 deported Polish physicians, and several wards for infectious, medical, surgical and pediatric diseases, the staff of which was composed of 5 other deported Polish physicians. There were also a laboratory and a pharmacy. The activities of the Polish staff of doctors were controlled by Russian local District Health Authorities.

The Polish medical staff† took an active part in the observation and treatment of our tularemic patients. The Russian health authorities also helped us in our work.‡

One hundred and twenty-one cases of tularemia were observed in the hospital of Asino during July and August, 1941. There were 63 ambulatory patients (40 Russians and 23 Polish citizens) and 58 hospital cases (28 Russians and 30 Polish citizens). There were 81 females (66.9%) and 40 males (33.1%). Their ages ranged between 6 and 63 years; 50 were under 20 years of age (among them 32 children below 15 years); 53 patients were between 20 and 40 years; 18 patients were above 40 years of age. More than half of the patients (63) were peasant or field workers. One fourth of the patients (30) were children going to the village public school. There were also among the patients 12 men who worked in the saw-mill of Asino, 14 watchmen, coachmen and clerks, and finally 2 children below school age.

Many other cases of tularemia occurred in the neighboring villages during July and August, 1941. This was evident from the information supplied by our patients. Without any doubt the 121 cases reported in this paper constituted only a part of a much larger epidemic of tularemia in this district. Since we had no access to the statistics of the Russian District Health Authorities, we were not able to ascertain the exact extent of the epidemic.

Epidemiology. Among the most striking and unusual features (even in Russia) of this epidemic were its massive and sudden outbreak, its very short duration, and its uniform type. Although scattered cases of the ulceroglandular form of tularemia were treated in the hospital during the period between July, 1940, and July, 1941, the true epidemic outbreak started within the first few days of July, 1941.

* "Tomasinlag" is an aggregate of many camps of confinement and forced labor of the Tomsk-Asino District. It was run by NKVD (Russian Security Police) and was populated mostly by Russian political and criminal prisoners.

† The author wishes to express his deep appreciation for the work which was done by the Polish medical staff:

Dr. J. Ber helped us very much in collecting the epidemiologic data. The late Dr. J. Olecka, as well as Drs. Brunne and Szpigelman participated in the routine hospital work. Drs. Dziewulski, Fajman and Kadysiewicz observed the ambulatory patients and permitted us to review their cases. Mgr. Keiler did all the laboratory work.

‡ The Division of Infectious Diseases of the Medical Faculty of the University of Tomsk, headed by Prof. Minkiewicz, delegated an entomologist to the Settlement and supplied us with adequate amounts of tularemic antigen for agglutination tests and tularin for allergic tests. Prof. Minkiewicz visited the settlement and gave us clinical advice.

Dr. Litwinow, head of the Russian local District Health Authorities, brought us into contact with the Division of Infectious Diseases of the Medical Faculty of the University of Tomsk.

At this time 6 cases of tularemia were brought to the hospital. From then on, the number of cases increased rapidly, so that 11 more cases were admitted during the second 10 days and 19 new cases during the last 10 days of July, 1941. The peak of the epidemic was attained during the first 10 days of August, when 45 new cases were admitted. At this time our small hospital of 100 beds was practically filled to its capacity with tularemic patients. After the peak was reached, the epidemic subsided rapidly. During the second 10 days of August, 22 new cases were admitted and during the last 10 days of August only 6 new cases. During the first few days of September only 3 new cases were admitted, and finally the epidemic stopped as rapidly as it came. (During the epidemic, 9 ambulatory cases were observed in addition in the settlement; the dates of the beginning of the disease in these cases could not be determined).

The outbreak of the epidemic started apparently in the collective farms (kolchoz) Nowikowka and Foetistowka. Rapidly the settlement and village of Asino, as well as the settlement of Jaja were invaded.

The morbidity rate in Asino was 1.8%. Among the 1840 persons living in the settlement of Asino 33 contracted tularemia during these 2 summer months. The highest incidence of tularemia occurred, however, in the neighboring settlement of Jaja, where, out of 460 persons, 52 (11.3%) developed this disease within 50 days (from July 10, 1941 to August 30, 1941). There is no record in medical literature of tularemia in which the morbidity rate was as high as this one.

According to the epidemiologic investigations of the Public Health Authorities of the Novosibirsk Province, (Karpov[10]) and information obtained from the entomologist of Tomsk University, the main source of tularemia in this area is always the water-rat (*Arvicola amphibius*). The water-rats leave their holes after floods, which in Siberia occur in May and June, and take refuge in the brushwood along the shores of the river. In 1941 an unusual number of dead water-rats were found on the shores of the Czulym river and adjacent stagnant waters. This could indicate an epizootic among these rodents in the summer of 1941.

Although most cases of tularemia in Soviet Russia are reported in connection with rat-hunting or working with rat-pelts, this direct mode of infection could not be accepted for our cases. All of our tularemic patients were asked about direct contact with rodents and all of them flatly denied any direct contact with water-rats, squirrels, rabbits or hares. Meadow-mice did not play any rôle in the Asino epidemic of tularemia. Usually, in such cases the stack of grain is infected by tularemic mice, and the tularemia bacilli are transmitted to man by inhalation of infected grain dust during thrashing, or by ingestion of bread made of infected grain. This indirect method of transmission occurs only in fall and winter, so that it does not apply to our cases. Moreover, the clinical features of our cases indicate another portal of entry for the infection.

Tularemia may also be transmitted to man in an indirect way. An insect acting as a vector bites infected rats and subsequently man. This method of infection is accepted in the United States and in Russia for occasional cases of tularemia. However, neither in the United States nor in Soviet Russia has there been published a report of an epidemic outbreak of this kind. The only report similar to this was made by Olin[16,17] in Sweden. He described an outbreak of tularemia among 115 peasants walking barefoot and bitten by mosquitoes in Gaevleborg district in 1937.

In our epidemic the following facts indicate that tularemia was transmitted to man not directly from rodents, but by insects acting as vectors. (1) None of our patients had any direct contact with rodents. (2) One hundred fifteen cases out of 121 developed the ulcero-glandular form of tularemia. The primary focus in 66.9% of the cases was situated on the lower part of the leg or on the foot. This excludes the direct way of infection from the rodents, in which case the hands are usually infected first. (3) The portal of entry of *B. tularense* was uncovered at the time of the infection. This was true of the cases in which the primary focus was located on the face, neck, hands, arms, legs and feet. The adults worked in the fields and meadows making hay or in saw-mills with their arms and legs uncovered and often barefooted; the children walked to the village school without shoes. (4) The peak of the epidemic corresponded to the peak of the development of small insects in the Czulym area (the end of July and August). (5) All the patients admitted frequent bites of small insects a few days before the outbreak of the disease.

These facts suggest that insects acted as vectors in this epidemic. It must be conceded, however, that no definite opinion has been established concerning the type of the insect responsible. The entomologist of Tomsk caught many types of insects encountered in the area of the epidemic and examined them for the presence of *B. tularense*. Due to my unexpected departure from the place of deportation in September, 1941, I was unable to obtain the results of these examinations. However, since the examinations were made very late in the epidemic they would not have been very reliable.

The vector of this epidemic probably would not be found among the group of biting flies like *Chrysops* or *Stomoxis*, or among the ticks; the search for it should be made among the small insects, like mosquitoes, midges or *Simulia*.

The following evidence suggests this conclusion: (1) None of the patients recalled having been bitten by a fly; the bite of *Chrysops* or *Stomoxis* is painful and cannot be overlooked. (2) Most of the patients did not notice the primary focus until their attention was called to it. (3) No ticks were seen by the patients, and such ticks are found only in woods or on live-stock in Siberia. When present, the ticks in Siberia (mostly *Ixodes persulcatus*) bite in May or June, but not in August, as exemplified by the early estival Siberian type of tick-encephalitis. (4) Most of the patients were bitten by mosquitoes while making hay or weeding potatoes. (5) Almost all the patients stressed abundance of mosquitoes and midges at their place of work. (6) Among 32 children below the age of 15 years, who habitually walked with uncovered legs and barefooted, 30 (93.7%) were bitten on the foot or lower part of the leg, and only 2 (6.3%) on the face or hand. On the other hand, of the 83 cases of ulcero-glandular form of tularemia in adults 51 (61.4%) were bitten on the legs or feet, and 32 (38.6%) on the face, neck, hands or arms. The adults did not have their legs and feet regularly uncovered. This shows that insects responsible for transmission of tularemia bit first on the uncovered lower part of the legs. They bit the face, neck, hands, and arms only if legs were covered. This is typical for the mosquitoes. (7) The experiments of Philip, Davis and Parker[20] proved that the *Bacillus tularense* could be transmitted by mosquitoes (*Aedes vexans, Aedes stimulans, Aedes canadensis, Aedes aegypti, Theobaldia incidens*) and that it could live in mosquitoes for several weeks. Moreover Olin[18,19] (suspecting mosquitoes as vectors of tularemia in his epidemic

outbreak in Sweden) was able to prove the presence of *B. tularense* in *Aedes cinereus,* by the inoculation of an emulsion of these mosquitoes into guinea pig.

The possibility of transmission of tularemia also by midges (*Chironimidae*) or *Simulia* should be kept in mind because of the large swarms of these insects were present in the working places. Since these insects ordinarily bite higher (face, neck or arms), mosquitoes are the vectors of this epidemic deserving serious consideration.

Serologic and Immunologic Tests. Out of the 121 cases of tularemia, 114 were proven by serologic or allergic tests, or by both. A positive tularemic agglutination test in a titer higher than 1:100 was obtained in 79 cases; a positive allergic intracutaneous test was noted in 8 cases in which agglutination was negative or was not done. In 27 other cases positive agglutination test and positive intradermal allergic test were obtained.

A positive *agglutination test* with tularemic antigen was found in 106 cases. In 92 the test was performed by a classical method, using the tularemic antigen supplied by the Tomsk University (suspension of *B. tularense* killed with ½% formalin, containing 1 billion of *B. tularense* per cc.). Dilutions of 1:50, 1:100, 1:200, 1:400, and at times 1:800 were used. Positive reaction in a minimal titer of 1:100 was accepted as evidence of tularemia. Among 92 cases which gave a positive agglutination reaction, in 17 the titer was 1:100, in 9, 1:200, and in 66 cases, 1:400 or 1:800.

Table 1

Time of occurrence of positive agglutination and allergic tests in some cases of tularemia observed during the epidemic in Asino.

Case No.	Agglutination reaction in serum for tularemia		Intracutaneous allergic reaction for tularemia	
	Day of illness	Result of the test	Day of illness	Result of the test
1	10	negative	11	positive
	20	positive in a titer 1:200		
13	10	negative	10	positive
	16	positive in a titer 1:400		
31	13	negative	12	positive
	20	negative		
	26	positive in a titer 1:400		
35	17	negative		
	25	positive in a titer 1:400		
48	13	negative	9	positive
	21	positive in a titer 1:400		

In most of our cases, corresponding to the observations of others, the agglutination test became positive only in the third week, and gradually increased in titer thereafter. The incidence of the positive agglutination test in the second week was only 47% (9 tests out of 19); and in the third week, 96.5% (83 tests out of 86). Typical findings, which illustrate the late positive agglutination reaction are listed in Table 1.

In addition to the 92 positive agglutination reactions, which were obtained by the classical method, in 14 other cases the simplified rapid micromethod of Minkiewicz was used.

One drop of blood is hemolysed on the slide by the addition of a drop of distilled water. Two drops of tularemic antigen containing 10 billion bacilli in 1 cc. are added

Table 2

Classification of clinical forms of tularemia which were observed during the epidemic outbreak in settlements Asino and Jaja.

Clinical forms of tularemia	Number of cases	Percentage
I. Oculo-glandular form	2	1.7
II. Anginal (tonsillar) form	3	2.5
III. Typhoid form	1	0.8
IV. Ulcero-glandular form	115	95.0
a. Primary focus located on the lower extremity. Swelling of the inguinal and femoral lymphglands.	81	66.9
b. Primary focus located on the upper extremity. Swelling of the axillary and epitrochlear lymphglands.	18	14.9
c Primary focus located on the face or neck. Swelling of the cervical, submaxillary, supraclavicular or infraclavicular lymphglands.	16	13.2
Total	121	100.0

FIG. 1. Oculo-glandular form of tularemia.

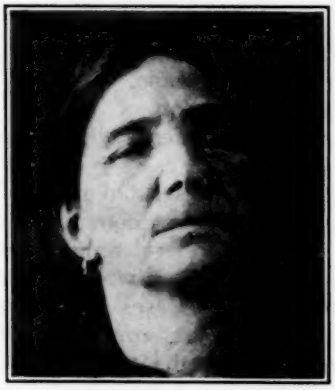

FIG. 2. Anginal (tonsillar) form of tularemia.

and mixed thoroughly. Controls are made simultaneously with the same blood added with physiological salt solution, with paratyphoid, typhoid, and brucella antigen. Fine-grained or coarse-grained agglutination in absence of the agglutination with control solutions occurring 1 minute after the addition of the tularemic antigen is accepted as evidence of positive or strongly positive reaction.

The test of Minkiewicz in the third week of the disease gave 100% of positive results.

Intradermal allergic tests with 0.1 cc. of tularin were made in 43 clinically evident cases of tularemia. The tularin which was used consisted of tularemia bacilli killed by heating at 70°C and suspended in physiological salt solution; the tularin was added with 3% glycerin, and contained 10 million of *B. tularense* in 0.1 cc.

Positive reactions were obtained in 35 out of 43 examined cases. In the third week of tularemia or later, the reaction was found positive as frequently as the agglutination reaction (12 positive tests out of 13). The advantage of the allergic intracutaneous test over the agglutination reaction was that it often detected the disease even in its earliest period. Out of 35 tests which were performed in the first 2 weeks, a positive response was obtained in 23, or in two thirds of the cases. Out of these 23 positive tests, in 15 the positive reaction was obtained at the end of the first week of the disease.

Classification and Symptomatology. All forms of tularemia, which are listed in the classification of Francis, were found in our epidemic. The classification of these 121 cases is tabulated in Table 2. The data listed in this Table show that the most common form of our epidemic of tularemia was the ulcero-glandular one, which was represented by 95% of cases. The remaining cases (5%) were composed of the oculo-glandular, the tonsillar and the typhoid forms of tularemia.

OCULO-GLANDULAR, ANGINOUS (TONSILLAR) AND TYPHOID FORMS OF TULAREMIA: The clinical picture of these forms was typical in our cases and did not show any unusual features.

The oculo-glandular form of tularemia was observed in 2 cases (Fig. 1). In these cases the primary focus was situated typically on the lower palpebral conjunctiva. Edema of the palpebral conjunctiva, chemosis, injection with subsequent ulceration, and suppuration of conjunctiva were associated with lacrimation and pain in the eye. The preauricular, submaxillary and cervical lymph glands were swollen. The patients had moderate fever lasting for 7 to 10 days, followed by several weeks of low grade elevation of temperature. There were no signs of the involvement of central nervous system. The course of the disease was benign, and complete recovery occurred after several weeks. The intracutaneous allergic reaction and the agglutination test in serum were strongly positive.

The anginous (tonsillar) form of tularemia was observed in 3 cases (2 boys of 14 and 16 years of age and 1 woman 57 years of age). This form of tularemia is well known in Soviet Russia and is due to the drinking of water from collections of standing water or wells infected by water-rats or mice. All 3 patients admitted drinking such water when making hay.

All patients showed a typical primary focus in form of an ulceration on the tonsils with subsequent necrotic or diphtheritic ulcer. The latter had a very protracted course with very slow healing, accompanied by a characteristic enlargement of the regional submaxillary and cervical lymph glands, which were very painful at the outset. A typical remittent fever, lasting for about 2 weeks, was followed by a low-grade elevation of temperature of long duration. The intracutaneous and the agglutination tests were strongly posi-

tive. The lymph glands underwent complete regression after a period of several weeks. In one case, however, the lymph glands suppurated and necessitated incision and drainage (compare Fig. 2.)

Pronounced leukocytosis was found in this case. Neither severe toxic symptoms nor involvement of central nervous system were observed.

The typhoid form was observed in only one case, a 17-year-old girl. Her course was typical and was characterized by a remittent fever of 3 weeks' duration, enlarged spleen, stupor during the first weeks of the disease, leukopenia with lymphocytosis and absence of eosinophils in the blood. No primary focus and no enlargement of lymph glands were found. The intracutaneous test with tularin was positive on the 6th day of the disease, and the tularemic agglutination test was positive in titer of 1:400 on the 21st day. This patient made good recovery.

THE ULCERO-GLENDULAR FORM was the most common and was characterized (apart from its usual features) by the central nervous system involvement and by the unusual location of the primary focus.

a. Involvement of the central nervous system was the most striking feature of this epidemic. It consisted mostly of early involvement of the meninges. This was observed in almost one-half of the hospitalized cases (28 out of 58). All these cases showed either signs of meningism or serous meningitis, and some of them in addition had signs of cerebral involvement in form of men-

Table 3

Location of the primary focus in 115 cases of ulcero-glandular form of tularemia during the epidemic outbreak in settlements of Asino and Jaja.

Location of the primary tularemic focus	Number of cases		Percentage
A. Lower extremity		81	70.4
a. foot	15		
b. leg	63		
c. thigh	3		
B. Upper extremity		18	15.7
a. hand	7		
b. forearm	5		
c. elbow	5		
d. arm	1		
C. Neck or face		16	13.9
a. supraclavicular or suprascapular region	3		
b. neck	7		
c. cheek	3		
d. chin	1		
e. nose	2		
Total		115	100.0

ingo-encephalitis. These rare observations are being reported in a separate paper[7]. The signs of the meningism or serous meningitis were usually transient, so that only one fatality was observed among these cases.

b. The primary focus was in each case of the ulcero-glandular type of tularemia in the form of a typical papule, later pustule, surrounded by an area of infiltration. Later a small oozing ulceration remained, which, in the absence of secondary infection, gradually dried and became covered with a scab. The surrounding infiltration in half of the cases disappeared after 1 to 2 weeks. In another half of the cases it lasted 2, 3 and 4 weeks before it underwent resolution. Regional lymphangitis was not seen among our cases. In 3 of the cases secondary small pustules developed around the primary foci and disappeared after a few days.

The location of the primary focus in the 115 cases of ulcero-glandular type of tularemia is given in Table 3.

The location of the primary focus in this epidemic is atypical and is not found in such extent in any other publication about tularemia, except in Olin's[17] cases. Nor in Soviet Russia has this type of epidemic been reported previously. This is evident, if one compares the location of the primary focus in our cases and in those reported by Russian authors (Table 4).

Figure 3 shows the primary focus on the neck, and a regional lymphadenopathy. Figure 4 shows a typical primary focus in form of a pustule on the lower part of the leg.

c. General constitutional symptoms, as described in the classical accounts of Francis[6] and his followers, were found in all early hospitalized cases of the ulcero-glandular form of tularemia. These were: acute onset of the disease with chills, prostration, toxic symptoms, severe headache and high fever.

The fever was remittent in a typical way. 40% of the cases had high fever type: 4 to 10 days of high fever up to 40°C, followed by several weeks of low-grade elevation of temperature. Another 40% of the cases had moderate fever: 3 to 7 days of fever up to 38 to 39°C, followed by 1 to 3 weeks of low-grade elevation of temperature. The remaining 20% of cases had recrudescent fever: 3 to 7 days of fever

Table 4

Frequency of the involvement of the lower extremity in the ulcero-glandular form of tularemia in Soviet Russia (according to Pokrowskajazi) as compared with the epidemic in Asino and Jaja.

Author	Place of the epidemic	Total Number of cases of ulcero-glandular form of tularemia	Number and percentage of cases showing the primary focus on the lower extremity.	
			Number	Percentage
L.M. Chatenewer	Glatma	164	7	4.3
L.M. Chatenewer	River Bialka	40	2	5.0
D.A. Golov	Ural	102	15	14.7
G.J. Sinaj	Kazachstan	32	4	12.5
	Total	338	28	7.2
G.B. Jerzy Glass	Asino and Jaja, Novosibirsk Province, Siberia	121	81	66.9

up to 38 to 39°C, followed after a short period of low-grade elevation of temperature and another recrudescence of fever up to 38 to 40°C, usually occurring on the 10th to 14th day of the disease. This recrudescence lasted for 2 to 6 days and was followed by another period of low-grade elevation of temperature.

No relation was found between the site of the primary focus and the type of fever. In most cases of tularemia involving the central nervous system usually high fever type was present.

d. Regional lymphadenitis was found in all 115 cases of the ulcero-glandular form of tularemia. The location of the lymphadenitis was listed in Table 2, which shows its distribution according to the anatomical features of the lymphatic drainage. The lymph glands were very painful at the beginning, but gradually underwent regression, in 3 to 6 weeks. In many instances the enlargement of lymph glands persisted for several months. Fig. 5 shows a typical picture of the enlargement of femoral lymph glands, which was found in two thirds of our cases.

Only in 9 out of 58 hospitalized tularemic cases did suppuration of the lymph glands necessitate surgical intervention (incision and drainage).

e. Blood picture. Red blood cells and hemoglobin showed in general no characteristic changes, although a slight microcytic hypochromic anemia was noted in many of the prolonged cases.

The white blood cell count at the beginning of the disease was almost constantly normal. In 29 of 35 cases, which were examined in the first week of the disease, the white blood cell count ranged between 3000 and 6000 cells per cmm. This was the normal range of white blood cell count in the population of settlements and adjacent villages of Siberia at that time, due probably to nutritional deficiency and malnutrition. The white blood cell count was increased above 7000 in only 7 cases, so that the average value of

FIG. 3

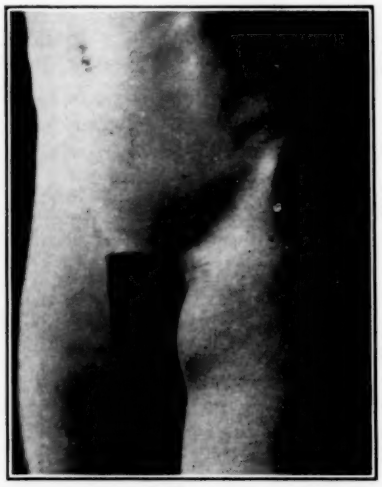

FIG. 4

FIG. 3. Ulcero-glandular form of tularemia, with primary focus located on the neck and regional lymphadenopathy.

FIG. 4. Primary focus located on the leg in a case of ulcero-glandular form of tularemia.

white blood cells in the first week of tularemia was 5600 per cmm. (average value of 36 cases).

Leukocytosis, which was described as a characteristic feature of tularemia, was found in our cases only in the 2nd or 3rd week of the disease, or later. In 11 out of 17 cases, examined at this time, leukocytosis was found, with values between 7000 and 28000 per cmm. The average of 17 cases was 10200 per cmm.

The differential count of white blood cells in our cases showed the following deviations of the normal: (1) Absence of eosinophils; this was found in the 1st week of the disease in 28 out of 35 (80%) and in the 2nd and 3rd weeks in 60% of cases. (2) Shift to the left; an increase in amount of immature cells above 5% was found in the 1st week of the disease in 32 out of 35 (91%), with an average value of 12%. In the 2nd or 3rd weeks of the disease the shift to the left was found in 14 out of 17 (80%), with an average value of immature of 7%. (3) Monocytosis; this was found in approximately half of our cases (in 18 of 35), with an average value of monocytes of 8% in the 1st week of the disease. (4) Lymphocytosis; this was found very often. In some cases it seemed to depend on the youth of the patient. On the other hand lymphocytosis was observed also in 12 adults.

f. Sedimentation rate was examined in 39 cases of tularemia. The micro-method of Panchenko was used. In the 1st week the sedimentation was accelerated in all 20 examined cases. Values between 13 and 44 mm. in the 1st hour were found, with an average of 25 mm. (normal values for this method range between 2 and 8 mm.). In the 2nd, 3rd, and 4th weeks of the disease the

FIG. 5. Femoral lymphadenopathy in a case of ulcero-glandular form of tularemia, with primary focus on the leg.

sedimentation rate was increased in 16 out of 19 cases, with values between 14 and 62 mm. averaging 28 mm. after the 1st hour. The highest values of sedimentation were found in cases of tularemia complicated by suppuration of regional lymph glands.

g. Complications. The strain of *Bacillus tularense* which was the cause of this epidemic showed definite neurotropic affinity. This is suggested by the frequent involvement of the central nervous system and by the almost complete absence of any other complications. None of the 121 cases showed pulmonary involvement. Cutaneous complications consisted only in a multiform erythema observed in 1 case and in a transient maculo-papulous exanthem observed in 2 other cases during the 3rd and 4th weeks of the disease. The renal involvement was seen in only one case, in which a previous glomerulo-nephritis was aggravated under the influence of the tularemia and resulted in uremia and death.

Treatment: Immune serum was not available for the treatment of these cases. Streptomycin was not yet known at that time (1941). Only symptomatic care could be offered. In spite of this inadequate regimen, 119 out of 121 cases recovered after a more or less prolonged course lasting up to several months.

The mortality rate was very low (1.7%) and corresponds to the rate observed in Soviet Russia. Only 2 fatalities occurred in 121 cases: one due to the exacerbation of a previous glomerulonephritis, resulting in uremia, another due to severe meningo-encephalitis.

Summary. One hundred and twenty-one cases of tularemia resulting in 2 deaths were observed during a short epidemic outbreak in settlements of deportation Asino and Jaja, Novosibirsk Province, Siberia, Soviet Russia, during the Summer of 1941. One hundred and fourteen cases were confirmed by serologic and, or, intracutaneous allergic tests, and 115 out of 121 belonged to the ulcero-glandular form of this disease.

Since no direct contact of infected persons with rodents could be traced and the primary tularemic focus was located in two-thirds of all cases on the leg or on the foot, the epidemic must have been transmitted by insects, probably mosquitoes. The source of infection was the water-rats populating the shores of the Czulym river at the time of infection.

The morbidity rate was tremendous in the settlement of Jaja, where 52 cases out of the entire population of 460 contracted tularemia, a morbidity rate of 11.3%. In the other settlement of Asino the morbidity rate was smaller, and averaged only 1.8% (33 cases of tularemia out of the population of 1840).

Another striking feature of this epidemic was an early and transient involvement of the central nervous system, consisting of signs of meningism, serous meningitis and at times meningo-encephalitis. Almost half of the early hospitalized cases of tularemia (28 out of 58) showed an unusual characteristic tetrad: (1) meningism or serous meningitis, (2) high fever, (3) primary tularemic focus in form of a small papule or pustule on the leg or foot, and (4) regional femoral or inguinal lymph gland swelling.

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PRINCIPLES IN THE MANAGEMENT OF CHRONIC NON-SPECIFIC ULCERATIVE COLITIS*

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The treatment of chronic non-specific ulcerative colitis is as poorly defined as is its etiology. Each theory as to its cause has led to a corresponding form of therapy. In turn, the good results that have followed each therapeutic procedure, irrespective of the other measures employed, have been interpreted as support for a particular causation. That accounts for the varying emphasis, both in etiology and treatment, on infectious, allergic, metabolic and psychogenic factors. In the more severe cases, however, without reference to the cause and largely because of its frequent good immediate results, ileostomy is commonly advocated.

None of these therapeutic procedures, however, or any combination of them often brings about a permanent cure. The relief that follows, no matter how complete, is usually of a temporary nature. In a review of the recent literature, covering 3639 medically treated cases followed from 1 to 10 years, including 148 of our own, only 8% obtained relief for an extended period, while 46% were admittedly unimproved and 5% died without operation (Chart 1). The remaining 41% showed some signs of improvement, but most of them remained more or less incapacitated and often developed a recurrence of activity. Of the unimproved cases 638 had an ileostomy. Thirty-four per cent of these died, often no doubt because of delay in resorting to surgery, and another 32% secured no significant relief. Of 184 finally subjected to a colectomy and followed, 27% died, while 54% may be regarded as cured; of the remaining 19%, improved or unimproved, it is probable that many had only a partial colectomy.

Were it not for the ileostomy stoma, with which the colectomized patients are left and which in most instances is permanent, this operation would seem to be an ideal therapeutic procedure. Furthermore, if done earlier in the course of the disease, before the general condition of the patient is markedly impaired, the mortality from this operation probably would be trivial. At present, however, colectomy necessarily is reserved for the otherwise hopeless cases. Even so, both Cattell[3] and Cave[4] have reported on ten year experiences with only a 10% mortality.

Preliminary to every colectomy, however, an ileostomy is necessary. The mortality from this procedure is higher because most clinicians agree to it only when the patient's condition is at its worst: when, in spite of temporary supportive measures, he is emaciated, chemically disorganized, more or less anemic and highly toxic. In the two-thirds that nevertheless survive the ileostomy, the condition of the patient

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† Aided by a grant from Mrs. Arthur W. Thompson.

usually improves: his appetite returns, the chemical disturbances are corrected, the diarrhea subsides, the ulcers heal and he gains weight. Although the improvement may not be permanent, due in many instances to complications and in others apparently to the natural course of the disease, one wonders by what means the ileostomy so often brings about a subsidence of the cases reported a year ago, to secure results comparable to those obtained by surgical ileostomy. It seems probable, therefore, that at least one of the factors in the beneficial effects of a surgical ileostomy lies in withholding from the colon the small intestinal contents. This does not imply that the small bowel contents are abnormal, though they may be; only that, under the con-

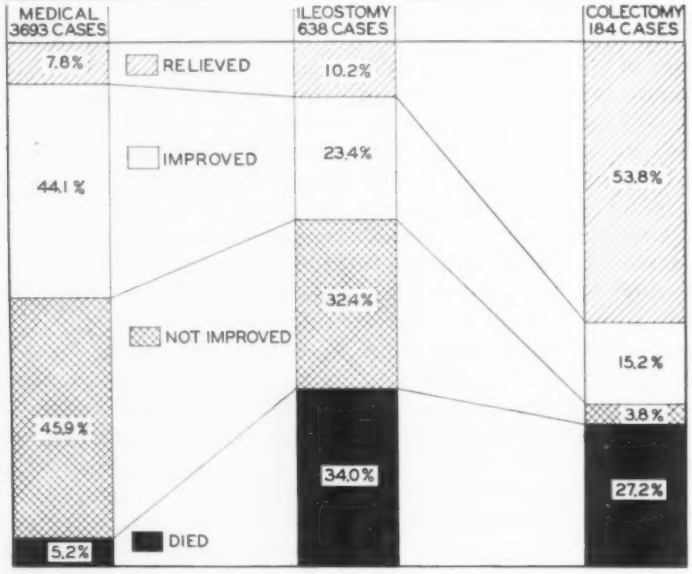

FIG. 1.—Results from therapy in chronic ulcerative colitis patients.

immediate disturbances.

With the idea of determining whether or not the relief is due merely to the diversion of the intestinal current, Machella[6] tried out a less hazardous procedure, a so-called "medical ileostomy": intubating the intestine to a point just short of the disease process and withdrawing by constant suction the residual material. By such a technique, combined with a high protein and high calory diet but uncomplicated by the use of antibiotics or other medicaments, he was able, in a series of 12 conditions of the disease, they are disturbing to the colon.

A careful study of small intestinal functions and its contents in patients with ulcerative colitis has not been made, but data are available to indicate an impairment in the absorption of protein products (Zetzel, Banks and Sagall[9]; Elsom, Dickey and Chornock[5]; Benson, Brown and Seldon[2]). Also in some instances we, as well as others, have found, on roentgenological investigation, an intestinal hypermotility. Furthermore, although we did

not appreciate its significance at the time and few actual measurements were made, we noted repeatedly that for the first few days after introducing an ileal tube a large amount of contents was aspirated, whereas later, when the patient's condition had improved, the amount was markedly reduced. Thus not only is the absorption of food material impaired in active ulcerative colitis, but the small bowel contents enter the cecum in excessive quantity.

Under normal conditions an increased ejection of intestinal contents into the cecum follows the ingestion of food and this is regarded as a factor in initiating mass movements in the colon. We may assume, therefore, that the excessive amount ejected in ulcerative colitis causes an increased irritability and contractility of the colon in that disease. Thus it would seem that we have a rational basis for the diversion of small intestinal contents from the colon, our first principle in the treatment of ulcerative colitis. At any rate we have an empirical basis, in that after both surgical and medical ileostomy the condition of the patient improves.

The second principle that we wish to emphasize, and a more important one, is the employment of a nutritionally adequate and easily absorbable dietary. In our experience to date this has consisted in the main of an enzymatic protein hydrolysate and dextrimaltose mixture* with added vitamins. This preparation was chosen because the amino acids, like the sugar, require no digestion and are readily absorbed; because quantities in excess of ordinary requirements are easily administered, and because, since it is a thin solution, such residue as reaches the terminal ileum is readily withdrawn. In spite of some loss of the mixture incident to its rapid transit through the bowel and its consequent aspiration during the first few days, the amount absorbed steadily increases and soon the residue contains no sugar or amino acids. Thus very quickly, as also is indicated by the improved nutrition and morale of the patient, the body's needs are met or exceeded. As further evidence of this in our series, the appetite returned, fever, when present, subsided, demonstrable ulcers healed, diarrhea lessened and the weight steadily increased. After 1 to 2 weeks it frequently was possible to add other food substances and remove the tube.

In view of the results from this program of rest to the colon and an effective diet, we have been encouraged during the past year to try out a series of 12 moderately severe, some quite severe, cases on such a dietary regimen alone. In 24 cases, 12 with and 12 without the tube, all observed within a 2-year period, we have secured satisfactory temporary results in all but 2: one of these, obviously allergic, showed some improvement but relapsed as soon as other foods were added; the other was not cooperative, and died. Four others have had mild relapses, all on an emotional basis, but quickly recovered; all are now gainfully employed. Thus it seems possible that the really essential therapeutic procedure for the immediate control of an attack, is that of securing the absorption of a high protein, high calory diet. In the more severe cases, however, because of the excessive irritation of the colon, this may be impossible unless for a time the colon is put at rest by one of the ileostomy procedures.

In spite of our emphasis on these 2 principles in management we do not wish to be understood to disregard procedures designed to combat emotional and infectious factors, or to overlook, in the presence of clear indica-

* Laboratory Product No. 197, consisting of 50% Protolysate and 50% dextri-maltose, generously supplied by Mead Johnson and Company.

tions, the ordinary measures for the control of anemia, allergic manifestations and blood electrolyte depletion.

The significance of emotional factors in the development of ulcerative colitis and its relapses is now well established. All observant clinicians are aware of this. Two thirds of Sullivan's[7] cases and one half of our total series of 157 showed some evidence of an unstable personality or of emotional crises preceding the onset of the disease. Almy and Tulin's[1] as well as White and Jones'[8] observations of the lower bowel through the sigmoidoscope indicate that the large intestine contracts when the subject is under emotional stress. This may be a purely reflex nervous phenomenon or it may be the result of an increase in the amount of small intestinal material injected into the cecum, such as is known to occur from excitement as it does after the ingestion of food.

At any rate coincident therapy directed toward the prevention, control and elimination of emotional factors is clearly indicated in all cases. This we have included in the management of all our patients, often seeking the help of the psychiatrists. Its share in the favorable results obtained is difficult to determine, but we suspect that it has been of great assistance and that it accounts to some extent for the good results reported after various other types of therapy.

Likewise infection undoubtedly is an important factor in the total picture of non-specific ulcerative colitis. It is inconceivable that this should not be so, since the feces consists in large part of microorganisms and the mucosal surface of the colon is not intact. Infection surely accounts for certain features of the disease, especially some of its complications, but it has not been demonstrated that any particular organism is the primary etiologic agent. In any event, when the patient is febrile or shows other systemic signs of infection, the antibiotics and chemotherapeutic agents are indicated. Furthermore, since their administration orally and per rectum has seemed effective in the hands of some clinicians, we venture the suggestion that their action might be enhanced if they were administered through a tube directly into the lower ileum or cecum, thus reaching the affected area in more concentrated form. Their general effect, in our experience, however, has not radically altered the primary bowel lesion, and without them, in the uncomplicated cases, we have secured equally satisfactory results.

Summary and Conclusions. Thus we have presented briefly certain so-called principles, especially rest to the colon and superalimentation, for the treatment of chronic non-specific ulcerative colitis. In advocating intubation as a means of bringing about colon rest, we fully appreciate its difficulties, its strain on the subject and the time, skill and patience required of the physician, but at least its limited employment in our hands has seemed to demonstrate one of the factors that tends to prolong and aggravate the disease. Fortunately, as a practical procedure, it is not usually required if a fully adequate and easily absorbable diet is administered. Such a dietary regimen is not original with us, but our experience has served to emphasize its maximal importance and its practicality. At the same time we have approved the employment of all measures calculated to allay or remove emotional disturbances, to control infection and to overcome anemia, allergic reactions and abnormalities in the chemical constituents of the blood.

Until its specific etiology is established, be that a bacterium, a virus, some metabolic fault or some other factor, a cure for chronic non-specific ulcerative colitis, aside from colectomy,

seems improbable. Otherwise the most that can be hoped for is relief of the immediate attack. If this can be obtained by measures other than surgical ileostomy, fewer patients will die and fewer of those who survive will be burdened permanently with an ileostomy stoma.

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HEATING OF HUMAN TISSUES BY MICRO WAVE RADIATION*

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Due to a slow rate of penetration, the heat furnished by most clinical methods of heat therapy is relatively ineffective in raising deep tissue temperatures. Short wave diathermy, the only available procedure for deep and rapid heating, also induces generalized effects and is, therefore, not easily adapted to the heating of localized masses of tissues. Since deep heating is only successfully accomplished through the medium of high frequency electrical energy, numerous attempts have been made to apply for therapeutic purposes the very high frequencies near the infra red region of the spectrum. Hemmingway and Strenstom[6] have discussed the possibility that deep and local heating could be accomplished by utilizing the optical properties of these short wave lengths. Krusen *et al.*[7] have described a commercial instrument and analyzed the physical properties of the electrical energy produced in radar systems. The results of their dog experiments indicate that these waves would provide a useful clinical tool. In this respect several investigators[4,5,8] have reported results which suggested that no deleterious effects are induced in personnel exposed to radar radiation.

Methods. All 9 subjects were healthy, vigorous individuals. Two males were in their twenties, another 2 in their thirties, and the remaining 2 in their sixties. Of the females, 2 were in their twenties and the third in her forties.

The experimental procedure briefly was as follows: Each subject rested quietly for about 1 hour in a room with a temperature of approximately 23° C. Control observations were made during the succeeding 15 minutes and then thermocouples were removed from the thigh area to be treated. Immediately after a 15 or 30 minute period of exposure in the radiation field of a microwave generator (the magnetron tube oscillated at a frequency of 2450 megacycles per second—wave length 12.2 cm.), the thermocouples were replaced and the cooling of the tissues observed for periods of 30 to 130 minutes. The thermocouples were of copper-constantan and a type K, Leeds & Northrup potentiometer was used to measure the emf developed. Five surface thermocouples were placed on the area treated and 4 additional couples were placed at lower levels of the same leg and at corresponding points of the other leg. In a number of experiments additional thermocouples were distributed over the body, particularly on fingers and toes. To measure deep and superficial tissue temperature, hypodermic needles were inserted in the thigh, thermocouples threaded through them and the needles withdrawn, leaving the couples in place. Calibrated clinical thermometers were used to obtain rectal temperatures.

Microwave energy was directed by a 4-inch hemisphere (A), a 6-inch hemisphere (B), or a 4-inch corner or angle director (C) placed at a distance of 5 cm. from the thigh surface. Power outputs were 25, 50 or 80 watts; of the 17 experiments employing the 6-inch director, 3 were with 25 watts, 11

* Aided by a Grant from the National Foundation for Infantile Paralysis.
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with 50 watts and 3 with 80 watts. The remaining 6 experiments were equally divided among A and C directors at 50 watts. The preponderance of 50 watt exposures was related to employment of this dosage in current clinical trials of the efficacy of this mode of therapy.

Results. The temperature gradient from the surface of the thigh to a depth of 56 mm. is presented in Table 1. The consistent break in the temperature gradient at both 3 and 30 mm. was indicative of the presence of fascial planes at these levels. From 30 to 56 mm. the temperature appears to be at a constant level with only minor fluctuations. The general pattern of the gradient in the control observations is in essential agreement with results reported by Bazett and McClone[2] and Barcroft and Edholm,[1] although the actual values are different. These discrepancies are undoubtedly related to the great variability observed in deep temperatures in different muscles and at different horizontal levels of the same muscle. These factors have been discussed in detail by Buchthal *et al.*[3] The second set of gradients was obtained during the cooling period at the time when deep muscle temperatures (30 mm. plus) were essentially at control levels. Although a normal gradient pattern was observed from these depths to the skin, it was at a much higher absolute temperature. The heat content of the outermost 25 mm. of tissue was still high and heat losses were occurring from this mass.

The maximum temperatures observed at 3 depths of the thigh, surface (0 mm.), subcutaneous (4-15 mm.), and muscle (over 30 mm.) following the heating of the tissue, are shown in Table 2. Due to the properties of micro wave radiation it is impossible to measure temperature changes during the period of heating and, therefore, the maximal temperature must be arbitrarily presented as an indication of the change in tissue temperature. The rise in surface temperature was roughly equivalent with the B director at 3 generator outputs. This 3 to 5°C. increase correlated with the subjective evaluation of a mild and pleasant heating volunteered by patients and subjects. Erythema was observed in only a few instances and this with other directors and higher powers. The alterations in the subcutaneous temperatures were most striking with both A and B directors. In the majority of instances these values were higher than simultaneously determined muscle tem-

TABLE 1. — TEMPERATURE GRADIENTS IN THE TISSUES OF THE LATERAL ASPECT OF THE THIGH

Depth mm.	Pre-treatment °C.	Post-treatment* °C.
0	31.4	33.3
3	30.7	32.7
6	31.6	33.4
9	32.5	33.9
13	32.4	34.7
16	33.8	35.0
19	33.5	35.3
22	34.6	35.7
25	34.6	36.0
28	35.5	35.4
31	35.0	36.0
34	35.9	35.9
37	35.7	36.2
41	36.1	36.2
47	35.9	36.2
56	36.1	— — —

*Obtained at cessation of experiment (mean time, 57 minutes) when deep muscle temperatures had returned to control levels.

peratures. Muscle temperature could be elevated by exposure to greater generator outputs (Table 2 and Figure 3), but was accompanied by high subcutaneous values. At a power output of 50 watts a mean change of 9.3°C. in the subcutaneous tissue was found in 2 experiments. In 2 experiments with the small A director, values similar to those of the larger circular B director were obtained.

The elevation of deep tissue temperatures induced by micro wave radiation was maintained for at least 30 minutes and up to 2 hours (Figures 1 to 5). On some occasions the temperature at the subcutaneous level was not increased so greatly as the muscular tissue (Figure 2). In this subject the subcutaneous thermocouple was rather shallow (4 mm.). As was to be expected, surface temperatures remained elevated for

TABLE 2. — ALTERATIONS IN TISSUE TEMPERATURES OF THE LATERAL THIGH WITH APPLICATION OF MICRO WAVE RADIATION (12 CM.) FOR 15 MINUTES

	"B" Director 25 Watts		"B" Director 50 Watts		"B" Director 80 Watts		"C" Director 50 Watts	
	Mean °C.	Range °C.	Mean °C.	Range °C.	Mean °C.	Range °C.	Mean °C.	Range °C.
Surface Temp.								
Initial	32.4	31.7-33.1	31.2	29.7-33.1	33.1	31.3-33.9	30.6	30.1-31.6
Maximal	35.6	35.2-36.6	34.8	34.4-36.4	36.4	36.0-36.8	35.6	35.4-35.7
Δ	3.2		3.6		3.3		5.0	
Subcu. Temp.								
Initial	32.5	32.0-33.0			32.2	31.8-32.9	32.4	32.3-32.6
Maximal	38.1	37.9-38.2			42.9	41.8-43.9	36.3	35.4-37.2
Δ	5.6				10.7		3.9	
Muscle Temp.								
Initial	35.3	34.4-36.1	36.1	35.1-37.3	35.3	35.2-35.3	35.0	34.8-35.3
Maximal	36.6	36.3-36.8	38.5	37.3-39.8	39.3	38.9-39.9	38.1	37.2-39.0
Δ	1.3		2.4		4.0		3.1	

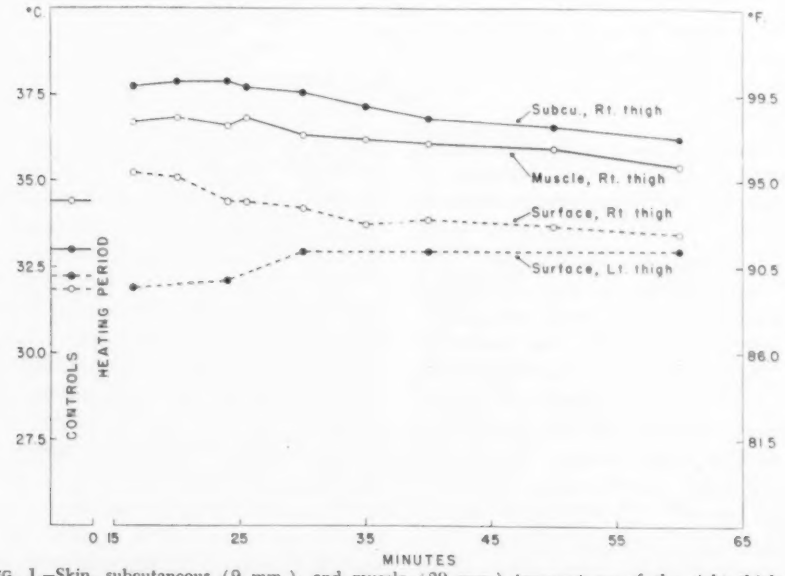

FIG. 1.—Skin, subcutaneous (9 mm.), and muscle (29 mm.) temperatures of the right thigh (lateral aspect) following treatment with microwave radiation. A 6 inch director with power output of 25 watts was applied 5 cm. distant for 15 minutes. Skin temperatures of the left, untreated thigh are also presented.

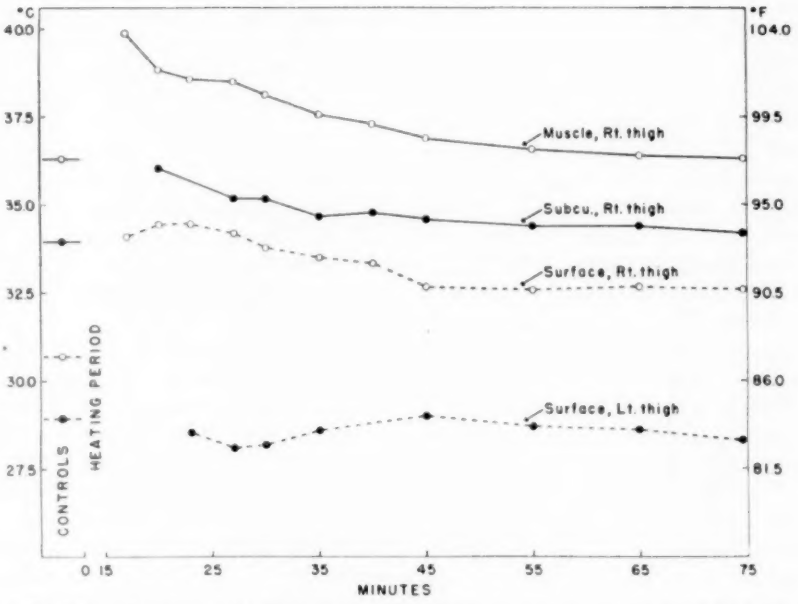

FIG. 2. Skin, subcutaneous (4 mm.), and muscle (35 mm.) temperatures of the right thigh (lateral aspect) following treatment with microwave radiation. A 6 inch director with power output of 50 watts was applied 5 cm. distant for 15 minutes. Skin temperatures of the left, untreated thigh are also presented.

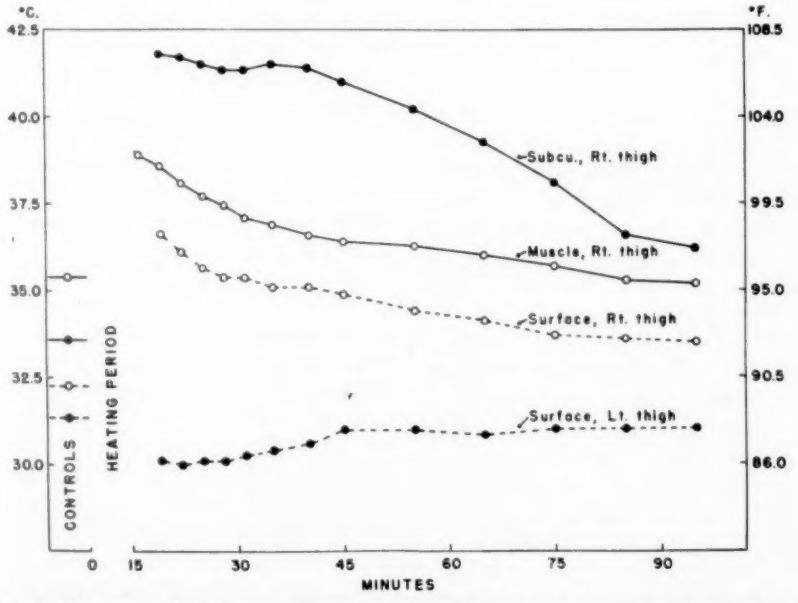

FIG. 3.—Skin, deep subcutaneous (17 mm.), and muscle (49 mm.) temperatures of the right thigh (lateral aspect) following treatment with microwave radiation. A 6 inch director with power output of 75 watts was applied 5 cm. distant for 15 minutes. Skin temperatures of the left, untreated thigh are also presented.

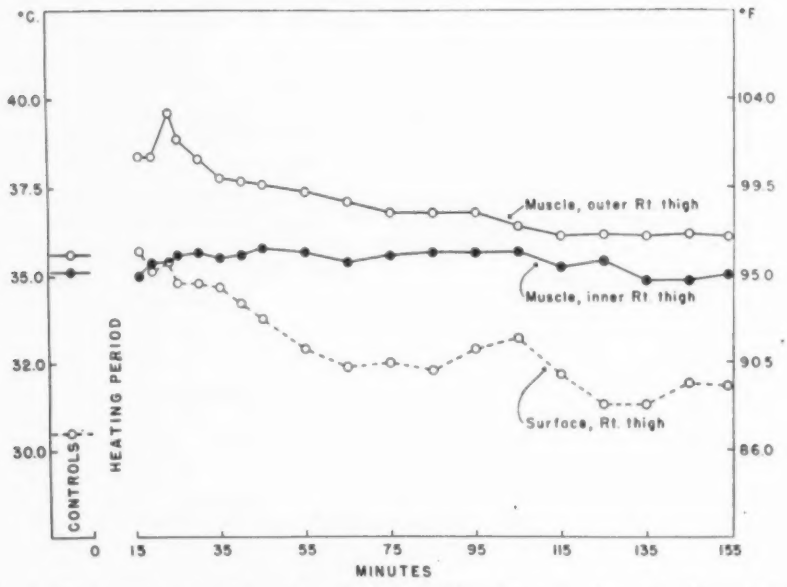

FIG. 4.—The temperatures of skin and muscle (32 mm.) lateral aspect and muscle (32 mm.) medial aspect of the right thigh following treatment with microwave radiation. The diameter of the thigh at these points was 170 mm. A 6 inch director with power output of 50 watts was applied 5 cm. distant for 15 minutes.

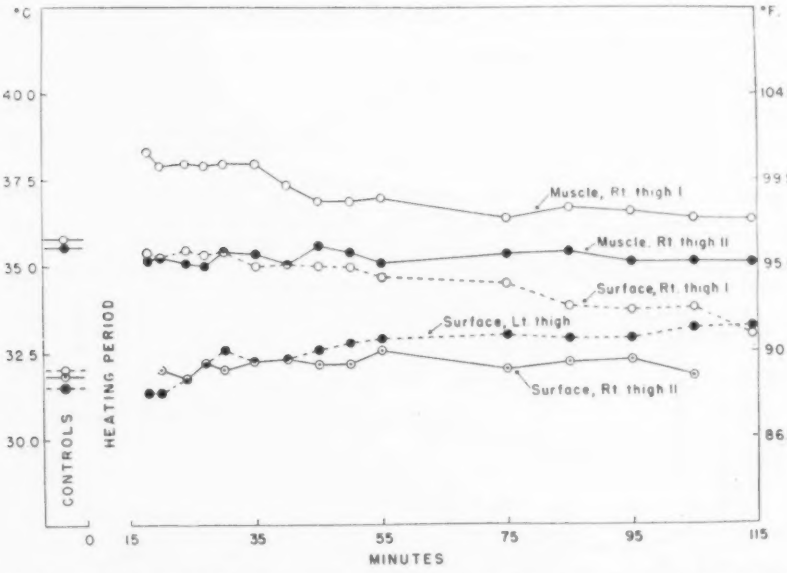

FIG. 5.—Skin and muscle (30 mm.) temperatures of the right thigh (lateral aspect) following treatment with microwave radiation. Number I values are from the center of the treated area while Number II values are 130 mm. lower and outside the area of the director. A 6 inch director with power output of 50 watts was applied 5 cm. distant for 15 minutes.

somewhat longer periods than was the case for the deep. The frequent occurrence of an initial transitory decrease in the surface temperatures of the left thigh may be indicative of a reflex vasoconstriction.

Deep heating was readily accomplished by micro wave radiation. In order to determine the extent of this effect additional experiments were conducted. When thermocouples were inserted at equivalent depths in the muscle tissue of opposite sides of a treated thigh, no positive evidence of heat transfer across the muscle and bone mass was noted (Figure 4). However, the muscle temperature of the inner surface of the thigh did not exhibit the gradual fall in temperature normally observed in resting muscles.[3] Since this phenomenon did not occur, it might be possible to interpret the small rise as indicative of some transfer, but in a repetition of this experiment on another subject this slight change was not duplicated. In Figure 5 a similar experiment is shown with a second thermocouple in the same muscle but 130 mm. lower and at a distance of 64 mm. from the edge of the director. Neither muscle nor surface temperatures at this point were elevated following treatment. In 2 other experiments surface and muscle temperatures were measured at various points within the area of the B director. Temperature determinations were within 0.3 to 1.0°C. Generally lower muscle temperatures were found nearer the periphery. Surface temperatures were not consistently different at any point within the area or during different experiments.

No evidences of generalized effects were observed. Rectal temperatures remained within ±0.1°F. of control values. Reflex vasodilation, determined by multiple toe and finger temperature measurements, was not induced.

Discussion. Exposure of the thigh to the radiation field of a micro wave generator resulted in definite changes in tissue temperatures. The effects were relatively local in that they were limited to the area of the director employed and did not penetrate to depths much beyond 60 mm. The output of the generator determined to a certain extent the depth of penetration and the site of greatest temperature alteration (Table 2). However, regardless of generator output the greatest changes in temperature were observed in the subcutaneous and contiguous muscle layers. With larger outputs, higher but not the highest temperatures were recorded in deep muscle. Whether this was due to actual penetration of energy to these depths or just to heat transfer was not definitely determined. That the latter may be involved is suggested by the high temperatures observed in the more superficial muscle layers. The normal gradient from subcutaneous to muscle tissue was reversed in practically all instances.

Osborne and Frederick[9] have reported the only other data on human subjects. They found a mean temperature of 40.1°C. at a depth of approximately 50 mm. Unfortunately, they failed to mention the power output of their generator. It was quite likely at least 80 watts. If such was the case, there would be essential agreement with the findings reported herein. A complete comparison of the effects of micro wave radiation on heating of tissues is not possible since Osborne and Frederick have presented only figures for one depth. Data presented by Krusen *et al.*[7] on dogs is essentially in agreement with the results on human tissue, if depth and not histological distinctions are employed for comparison. In both species the maximum elevations of temperature are observed at depths of approximately 20 to 35 mm. At other levels the effects are of a smaller order of magnitude.

The slight elevations of skin temperature observed (Table 2) are interesting in that subjectively patients report only a sense of pleasant warmth and are not conscious of the higher internal temperatures. Furthermore, erythema is noted in a very small percentage of cases and has been observed most frequently in those patients who have been perspiring prior to or during the early phases of the treatment. In one respect this illusion of mild warmth is dangerous, since many individuals, both patients and operators, believe that only a small amount of heat is being given and are tempted to increase the power output with possible ill effects in the deep tissues. This danger is especially likely to occur to those who are accustomed to short wave diathermy where skin sensation is the determining factor in dosage.

The cooling curves obtained are not susceptible to easy analysis since two distinct slopes were generally evident —an initial period of short duration with a rapid fall and a succeeding prolonged period during which the temperatures dropped at a much slower rate. These prolonged cooling curves offer opportunity for speculation regarding the influence of this mode of heating on the rate of blood flow through the heated tissue. Krusen *et al.*[7] have reported striking increases in venous flow in the dog's hind limb during and following treatment. However, rough calculations based on a mean temperature rise of 5°C. in human tissues indicated that cooling should have occurred within 15 to 30 minutes even with no increase in blood flow. But the cooling curves were much more prolonged, suggesting either no change or a small increase in the blood flow through the heated tissues. Information on this aspect is now being obtained.

Summary. The employment of high frequency electrical energy in the 12 centimeter band (2450 megacycles per second) of the electromagnetic spectrum provided a means of selectively heating local masses of tissue. The magnitude and depth of heating can be modified by varying directors and the power output of the generator. Maximal temperatures observed following a 15 minute period of heating, utilizing a power output of 50 watts and a 6-inch director, were 36.4°C. at the surface, 44°C. at subcutaneous levels, and 40°C. in muscle tissue. In the majority of the experiments the temperature gradient from subcutaneous tissue or muscle to surface was not modified greatly as a consequence of this mode of heating. However, in a large number of instances the subcutaneous to muscle gradient was reversed. High internal temperatures were secured with only incidental elevation of surface temperatures. No increases in rectal temperature were observed.

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CLINICAL EVALUATION OF PHENINDAMINE (2-METHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1-PYRIDINDENE HYDROGEN TARTRATE) AS AN ANTIHISTAMINIC AGENT

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An antihistamine substance may be defined as one "capable of diminishing or preventing several of the pharmacological effects of histamine"[4] by competing with it for a particular site of action or for the same tissue receptor, rather than by the production of diametrically opposite pharmacological responses. "This type of antagonism is reversible and one of the most specific in nature".[4]

Despite its specificity, it has been repeatedly shown that the reaction does not necessarily involve closely related chemical analogues but may be produced by a diversity of compounds, which, while sharing an antihistamine action in common, vary considerably in their pharmacological activity. For instance, certain of the benzhydryl alkamine ethers, to which class Benadryl belongs, show, in addition to their antihistaminic activity, an atropine-like action, not shared by equally potent antihistamine substances such as antergan, and closely related alpha-aminopyridine derivatives, of which Pyribenzamine is one.

While a number of compounds of the types just mentioned have exhibited a high degree of histamine-blocking action, many unpleasant side-effects have occurred in their application at the bedside. This has resulted in a widespread effort to find other substances, which retain the antihistamine property, but lack in greater or lesser degree undesirable toxic side-effects.

Phenindamine represents a compound of strikingly different chemical structure (Fig. 1), which shows appreciable antihistaminic activity.[2,3,7] In protecting guinea pigs from death due to exposure caused by inhalation of histamine spray, this drug proved to be about eight times as potent as antistine, twice as effective as Benadryl and one-half as active as Pyribenzamine.[7] In acute poisonings of small

laboratory animals, it is one-third to one-half as toxic as Pyribenzamine and about equal in toxicity to Benadryl.[2,3,7]

In other words, phenindamine represents an entirely new type of chemical compound with antihistamine activity, which compares favorably in animals with already well known antihistaminic substances, both as to toxicity and antihistaminic action. The present observations are directed towards determining its scope of action and possible usefulness in human beings.

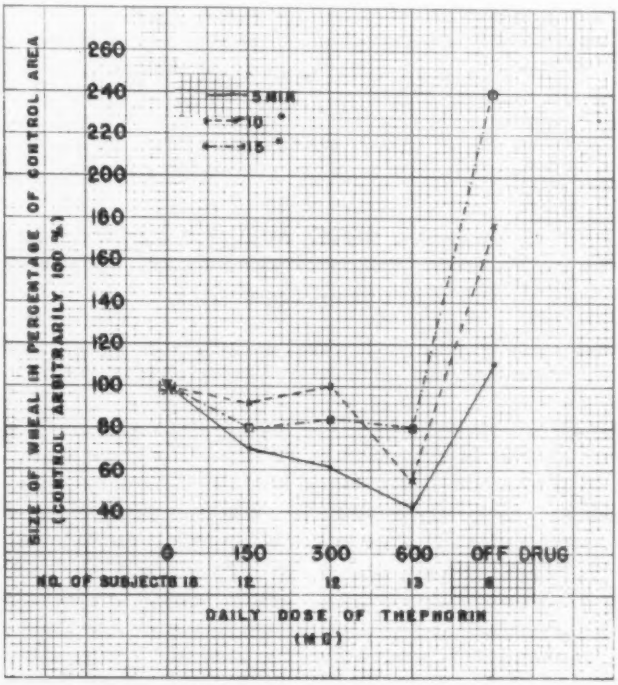

Fig. 1—The influence of phenindamine by mouth upon the histamine wheal reaction in the skin.

Methods and Materials. 133 "normal" persons, ranging in age from 18 to 61 years, and 136 patients with allergic disease between the ages of 21 and 68 years, have been the subjects of these observations. Under the term normal, we have included not only people without recognizable disease, but also a limited number of subjects with chronic osteoarthritis, moderate arteriosclerosis, and those attending a general medical clinic for minor illnesses. In all instances, subjects with any allergic manifestation or probable involvement of the autonomic nervous system were excluded from the "normal" group. Of the normal subjects, 100 were used to ascertain the frequency of untoward reactions to the drug. In the remaining 33, various bodily functions have been observed, while the subjects remained on a routine of living previously described in connection with the study of another antihistamine substance.[5] Intravenous glucose tolerance tests were carried out according to the method of Thorn,[8] as adapted to our own facility.[6]

Phenindamine* was administered in the form of 25 mg. tablets in doses varying

*Generous supplies of Thephorin, the Hoffmann-La Roche brand of phenindamine, were made available through Drs. Elmer Sevringhaus and W. T. Strauss of that organization, whose courtesy is herewith gratefully acknowledged.

from 75 to 600 mg. daily for periods varying from 1 to 20 weeks. For specific tests, such as glucose tolerance and electrocardiographic tracings unit doses of from 300 to 600 mg. were used.

Results. 1. THE ANTIHISTAMINE EFFECTS OF PHENINDAMINE. Indices of the antihistamine action of phenindamine action of phenindamine were its influence upon (1) the histamine wheal-and-flare reaction in the skin and (2) gastric acidity following a 7% alcohol meal.

tions of the wheal-and-flare reaction were made. Twelve of the subjects were successively given 150, 300 and 600 mg. daily for periods of two weeks at each dosage level, while the remainder of the subjects were utilized at one or more levels of administration for varying periods of time.

The method for performing these tests has been previously described.[1] Readings and measurements were made at the end of 5, 10 and 15 minutes. Each subject served as his own control.

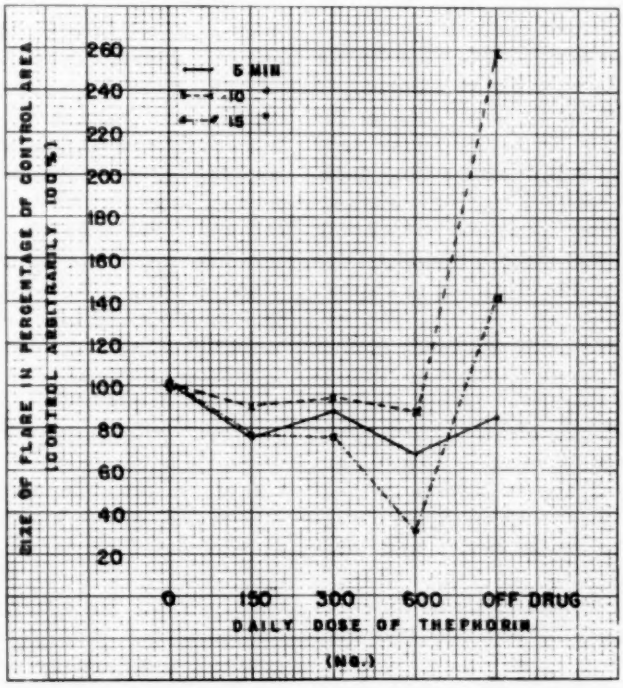

Fig. 2—The influence of phenindamine by mouth upon the histamine flare reaction in the skin.

1. Changes in the response of the skin to histamine following the oral administration of phenindamine. In 76 tests, the wheal-and-flare responses of 18 normal subjects were recorded following the oral administration of phenindamine in doses of 150 to 600 mg. daily for periods varying from one to eight weeks. In all, 76 determina-

Composite graphs of the areas of the wheals and flares thus obtained have been recorded in Figures 1 and 2 as percentages of the control values. Increasing doses of the drug influenced the size of the flare less than the size of the wheal, and at no dosage level was it possible to make these phenomena disappear routinely.

Several comments regarding individual responses may be apropos. In 15 subjects there was a steady decrease in the size of the wheal and flare as the dosage was increased, although the degree of change was always most marked with the initial dose of 150 mg. daily. In 2 subjects the dermic response to histamine was not appreciably altered by the oral use of phenindamine in the manner described, and in 1 the intensity of the reaction actually increased in spite of the drug. Of the 8 subjects studied in the "release" phase, *i.e.* one week after the drug was discontinued, 6 showed a dramatic increase in the size of the wheal and flare, while two developed responses similar to those seen in the control period. In two subjects there was complete suppression of the histamine flare while 600 mg. of phenindamine was being administered daily; in no instance was there a complete disappearance of the whealing phenomenon.

2. Changes in gastric acidity following the oral administration of phenindamine. 26 fractional gastric analyses following a 7% alcohol meal were performed on 6 subjects before and after the oral administration of phenindamine. In 4 subjects, the determinations were made before and after one week or more of treatment with each of the following daily doses of phenindamine: 75, 150 and 300 mg., respectively.

The values for gastric acid, both free and total, were lower in two subjects after two weeks each on 150 and 300 mg. daily of drug. In two more, the figures were at first lower, and in later tests higher than they were initially. In the remaining two subjects, there was no appreciable change in gastric acidity following the administration of phenindamine.

II. Non-Specific Effects of Phenindamine. A total of 33 normal subjects normal subjects were used in ascertaining the ability of phenindamine to influence various bodily functions. Unless otherwise specified the drug was given for prolonged periods of time at various levels of dosage, ranging from 75 to 600 mg. daily.

1. The influence upon glucose tolerance. Glucose tolerance tests were completed in relation to a single large dose of phenindamine in 9 instances, and after prolonged administration in 3 subjects. In 9 subjects, sugar tolerance was determined before and after the oral administration of a single dose of 300 mg. of phenindamine. The results have been described elsewhere in detail.[6] A similar study was attempted in 6 additional subjects following a single orally given dose of 600 mg. However, in each instance, the individual became nauseated and vomited before the test could be completed. Suffice it here to say that there were no appreciable changes in glucose tolerance as a result of such unit doses of phenindamine.

Three subjects were successively given daily doses of 75, 150, 300 and 600 mg. of phenindamine, respectively, for periods of not less than one week at each level of dosage. Before any drug was given and at the end of each period, an intravenous glucose tolerance test was performed. The results are graphically recorded in Fig. 3. It will be observed that no essential changes occurred in the glucose tolerance of these individuals as a result of the action of the antihistamine agent.

2. Influence upon the basal metabolic rate and the cardiovascular system. Serial determinations of the basal metabolic rate obtained in 33 subjects on a previously described regime of

living[5] were within normal limits following the use of phenindamine in widely varying doses (75 to 600 mg. daily) for periods of time ranging from 1 to 18 weeks.

The pulse rate, the blood pressure and the electrocardiograms of 30 normal subjects were not disturbed by large single or varying multiple doses of phenindamine.

3. Alterations in the formed elements of the blood. From Table 1 it is clear that the prolonged administration of phenindamine produces no significant changes in the blood count of normal subjects irrespective of levels of dosage between 75 and 600 mg. daily. The same statement may be made for all patients with allergic diseases in whom serial examinations of the blood were possible.

4. Chemical determinations upon the blood serum. As may be observed in Table 2, phenindamine employed over a wide range of dosage and for varying periods of time failed to cause significant alterations in the following determinations on blood serum: icteric index, the thymol turbidity, the alkaline phosphatase, protein and protein partition, urea nitrogen, creatinine, glucose, cholesterol and cholesterol esters. Van den Bergh reactions, not recorded in this Table, were routinely negative.

III. Experiences with Phenindamine in the Treatment of Allergic Diseases. In all, 136 patients with some In all, 136 patients with some type of allergy have been treated with phenindamine. The results are summarized in Table 3.

1. Hay Fever. Of 66 patients treated, 13 (20%) were not helped, 41 (62%) were partially relieved, and 12 (18%) obtained complete relief. Inasmuch as the severity of hay fever varies directly with the pollen count

Table 1. Blood Counts in Healthy Subjects Following Administration of Phenindamine in Varying Doses for Long Periods of Time*

		Phenindamine dosage					Differential Count (%)				
No. subj.	*No. determinations*	*Daily (mg.)*	*No. days used (average)*	*Hgb. (gms./100 cc.)*	*Erythrocytes (mill./cu. mm.)*	*Leucocytes (thou./cu. mm.)*	*P*	*L*	*M*	*E*	*B*
18	23	0	7 or more	13.8 (11–17)	4.32 (3.89–5.30)	6.12 (4.55–13.6)	57.8 (40–80)	36.7 (15–58)	4.0 (0–12)	1.45 (0–8)	0.05 (0–1)
1	1	75	7	13.0	4.50	7.50	60.0	35.0	3.0	2.0	0.0
1	1	100	5	15.0	4.37	5.40	70.0	28.8	1.0	0.0	0.2
12	28	150	31	13.6 (11–16)	4.19 (3.90–5.00)	6.71 (5.10–9.20)	54.6 (43–73)	42.7 (19–49)	2.2 (1–5)	1.2 (0–6)	0.5 (0–3)
1	2	200	14	13.5	4.15	7.53	67.3	30.0	2.0	0.7	0.0
13	26	300	21	13.6 (11–17)	4.20 (3.70–6.20)	7.60 (5.50–11.30)	63.8 (47–80)	32.2 (20–40)	2.7 (0–7)	2.3 (0–7)	0.1 (0–1)
6	8	600	7	13.3 (12–14)	4.40 (3.70–4.50)	8.30 (6.30–10.50)	56.0 (39–67)	40.5 (30–60)	2.4 (1–5)	1.0 (0–4)	0.1 (0–1)

* Figures in parentheses represent the range of values.

TABLE 2. CHEMICAL ANALYSES OF BLOOD SERUM FOLLOWING THE ADMINISTRATION OF PHENINDAMINE TO NORMAL SUBJECTS

No. Subj.	No. determinations	Phenindamine Dosage: Daily (mg.)	Phenindamine Dosage: No. Days Used (Average)	I.I.[1]	T.T.[2]	A.P.[3]	Protein[4]: Total	Protein[4]: Alb.	Protein[4]: Glob.	Urea N[5]	Creatinine[5]	Glucose[5]	Cholesterol[5]: Total	Cholesterol[5]: Esters
15	24	0	7 or more	5.4 (4.9–8.3)	2.4 (0.4–12.5)	3.1 (0.9–12.0)	6.6 (5.0–8.5)	4.3 (3.2–5.4)	2.3 (1.3–4.4)	12.9 (9.7–22.5)	1.3 (0.8–2.1)	105 (80–120)	230 (160–300)	145 (90–200)
2	2	75	7	5.2	0.6	3.0	7.2	4.7	2.5	11.5	1.2	108	244	164
1	1	100	7	5.1	1.9	4.0	7.0	4.0	3.0					
10	21	150	35	5.4 (5.0–6.0)	2.8 (0.3–13.6)	4.6 (2.0–6.0)	7.1 (5.6–8.9)	4.5 (2.8–6.0)	2.6 (1.6–3.0)	12.7 (6.8–23.5)	1.3 (0.8–2.1)	108 (93–127)	228 (185–330)	149 (70–220)
1	2	200	14	7.3	2.7	5.5	7.7	4.7	3.0	16.8	1.6	94	250	160
12	18	300	21	5.8 (5.0–9.2)	1.7 (1.0–3.4)	4.2 (1.0–10.2)	7.1 (6.0–9.0)	4.6 (3.5–6.0)	2.5 (1.5–4.4)	12.7 (7.0–17.0)	1.3 (0.9–2.3)	105 (83–116)	224 (146–340)	146 (100–230)
10	17	600	7	5.3 (5.2–5.7)	1.8 (0.9–2.7)	4.4 (3.0–7.0)	6.9 (5.2–7.8)	4.5 (3.5–5.6)	2.4 (1.5–3.3)	12.8 (9.5–15.9)	1.4 (1.1–2.1)	100 (87–109)	206 (164–272)	142 (110–182)

[a] Figures in parentheses represent the range of values.
[1] I.I.=Icteric index
[2] T.T.=Thymol turbidity
[3] A.P.=Alkaline phosphatase
[4] Expressed in per cent
[5] Expressed in mg. per 100 cc.

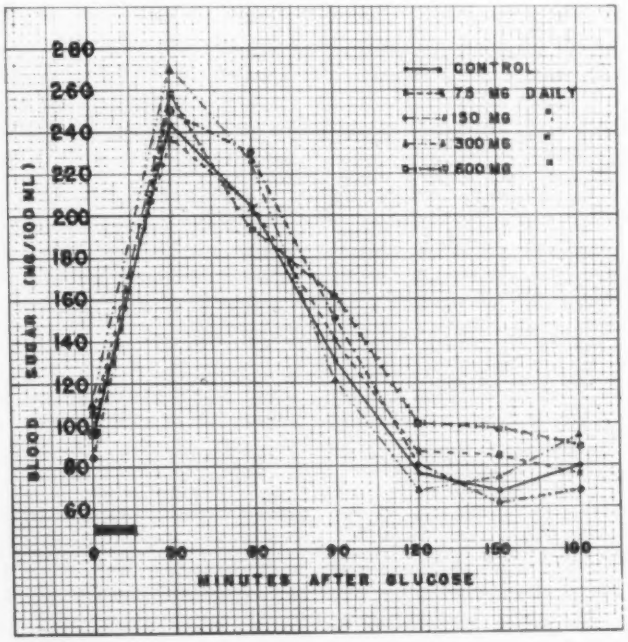

Fig. 3—Averaged glucose tolerance curves in 3 subjects before and after treatment successively with phenindamine in the daily dose noted. (Each dosage level was continued for at least 1 week in each subject).

in the air, we ran simultaneously a series of control observations in patients to whom a placebo was administered; 5% of these controls were symptom free, 30% improved while taking placebo and 61% remained in *statu quo*. In order to evaluate the results in terms of an antihistamine substance of known potency, a number of patients were given Benadryl and observed concurrently with those receiving phenindamine. Of these, 21% obtained complete relief, 59% partial relief and 20% no relief.

observed in each of 7 patients. These necessitated the discontinuance of the drug in two who received 75 and 250 mg. daily, respectively.

3. Bronchial asthma. Only 1 of 24 cases of bronchial asthma was relieved through the use of phenindamine (Table 3). However, in most instances, patients received the drug only at the time of their attacks. In 4 subjects, phenindamine was tried in a dose of 200 mg. daily as a prophylactic against attacks. In this connection it proved to be far inferior to Benadryl, the mild

TABLE 3. RESULTS OF TREATMENT WITH PHENINDAMINE IN 136 PATIENTS WITH ALLERGIC MANIFESTATIONS

Condition	*Total*	*Result*					
		*CR**		*I**		*NR**	
		No.	*%*	*No.*	*%*	*No.*	*%*
Hay fever	66	12	18.2	41	62.1	13	19.7
Allergic Rhinitis	25	5	20.0	9	36.0	11	44.0
Asthma	24	1	4.2	4	16.7	19	79.1
Urticaria—acute	16 3	6	37.5	8	50.0	2	12.5
Miscellaneous	5	1	20.0	2	40.0	2	40.0
Totals	136	25	18.4	64	47.1	47	34.5

* C.R. = Complete relief,
I. = Improvement and
N.R. = No relief

Phenindamine was employed in the hay fever subjects for periods of from 15 to 120 days in daily doses of from 75 to 150 mg. Side effects were present in 22 of the 66 patients, but in 6 were so mild as to disappear while the same daily portion of drug was continued.

2. "Vasomotor Rhinitis." Of 25 subjects with this condition (Table 3), 5 (20%) were completely relieved, while 44% were unimproved. All patients were started with 75 mg. of the drug daily; if there was no appreciable effect, the dose was increased until improvement occurred or until 250 mg. were used daily without relief. The periods of observation varied from 7 to 120 days. Some side effects were sedative and moderate antispasmodic action of which often protects the asthmatic completely for such time as it may be continued.

Seven of the 24 subjects showed some mild reaction to the drug, in no case sufficiently distressing, however, to prevent continuation of treatment.

4. Urticaria. Three of the 16 cases of urticaria were acute and 13, chronic (Table 3). It was difficult to tell with certainty whether or not the drug influenced the acute cases, although a clinical impression prevailed that the course of the condition was shortened. Of the chronic cases, complete or partial relief occurred in approximately 87.5% on daily doses ranging from 75

to 150 mg. Improvement occurred neither as rapidly nor as completely as with Benadryl to which the pruritus always yielded, probably in part due to its mild sedative action.

5. Miscellaneous conditions. Two cases of contact dermatitis were improved by phenindamine in daily doses of 75 and 100 mg., respectively, continued for 14 and 25 days, respectively. One patient with Fox-Fordyce's disease, in whom the itching was previously controlled by Benadryl, obtained no relief from phenindamine. One patient with a food allergy was not relieved following 14 days of treatment with 75 mg. daily. One patient with migraine of undetermined etiology was improved by unit doses of 25 mg. given in the very beginning of the individual attack.

IV. Toxic Effects of Phendamine. The toxic reactions to phenindamine phenindamine were recorded in a group of selected subjects and in all of the patients who received the drug therapeutically. One hundred subjects were included in the first study; they were chosen with a view to eliminating allergic conditions and any disturbance of the autonomic nervous system. The results with this group of subjects, who received daily doses of phenindamine ranging from 75 to 600 mg. for periods of from 1 to 6 weeks have been fully detailed elsewhere.[9] 42% of the group evidenced some untoward effect. The incidence varied directly as the dose of drug used. When 75 mg. were taken daily, approximately 15% showed some reaction. With the average therapeutic dose of 150 mg. daily, the incidence of side reactions was 25.0%. When used in similarly selected and treated subjects, the corresponding incidence of reactions to Benadryl and Pyribenzamine was 64% and 64%, respectively.

The incidence of symptoms due to phenindamine in the descending order of their frequency was dryness of the mouth, insomnia, constipation, dizziness, jumpiness or jitteriness, burning of the conjunctivae, intestinal cramps, drowsiness, weakness, and palpitation. Five subjects refused to continue the drug because of the severity of the side effects, but in none of these was the dose less than 300 mg. at the time it was stopped. In the smaller doses, insomnia and gastrointestinal symptoms were in the foreground. Most of the sensorial and circulatory symptoms occurred only when the largest doses were used.

Of the 136 patients who received phenindamine in a therapeutic range of

Table 4. Side Effects in 34 Patients Receiving Therapeutic Doses of Phenindamine

Symptom	*No. times observed*	*Symptom*	*No. times observed*
Dizziness	11	Headache	2
Drowsiness	9	Cough (?)	2
Dryness	9	Palpitation	2
Insomnia	7	Abdominal cramps	1
Nausea and vomiting	5	Nervousness	2
Blurred Vision	4	Weakness	2*
		Anorexia	1
		Total	55

dosage (75 to 250 mg. daily), 34 developed some unpleasant manifestation, and enumerated a total of 55 complaints attributable to these side reactions (Table 4). These are recorded in the descending order of their frequency in Table 4.

Discussion. Phenindamine differs in chemical structure and in pharmacological action from the majority of antihistamine substances previously used in clinical medicine. In the latter regard, quite in contrast, for instance, to Benadryl and Pyribenzamine, it antagonizes the pressor responses to epinephrine, an action completely independent of its antihistamine effects.

From our observations to date, several conclusions may be drawn regarding its clinical application in allergic states:

1. It is about one-half as toxic as Benadryl and Pyribenzamine.

2. For the most part it lacks the sedative action of Benadryl and does not share its weak atropine-like effect.

3. In the management of hay fever, it is approximately as effective as Benadryl.

4. In both vasomotor rhinitis and in asthma it is less useful than Benadryl, although in selected cases proves of value where the latter causes extreme drowsiness.

5. Satisfactory relief is obtained in a high percentage of the cases of chronic urticaria, although equal results have been reported with Pyribenzamine and better results with Benadryl. However, both the latter drugs have a greater tendency to undesirable side effects which may make phenindamine the drug of choice in many patients.

Summary. 1. Phenindamine (2-methyl-9-phenyl-2, 3, 4, 9-tetrahydro-1-pyridindene) represents a new type of compound with an overall antihistaminic activity in the human being which is about one-half to two-thirds that of either Pyribenzamine or Benadryl.

2. The allergic diseases which have responded to its application include hay fever, acute and chronic urticaria, and vasomotor rhinitis, somewhat in the order named. In these regards, its action follows the general pattern already observed for such commonly recognized antihistaminic compounds as Benadryl and Pyribenzamine.

3. The overall incidence of reactions to the use of phenindamine lies between 25 and 40% or about two-thirds to one-half that observed for either Benadryl or Pyribenzamine.

4. It seems likely from present comparative observations that no one antihistaminic substance will be useful in *all* cases where such compounds are applicable, but that individual variations from patient to patient may justify a "trial and error" method of selecting the most suitable preparation for the case in question.

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GLUCOSE TOLERANCE: II. EVALUATION OF GLUCOSE TOLERANCE IN LIVER DISEASE AND COMPARISON OF THE RELATIVE VALUE OF THREE TYPES OF TOLERANCE TESTS

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Since Hamman and Hirschman[16] first described the one-dose oral ("standard") glucose tolerance test and suggested its use as a diagnostic aid in diabetes mellitus, many disease processes other than insulin deficiency have been shown to exhibit disturbances in carbohydrate metabolism resulting in a decreased glucose tolerance. As our knowledge of carbohydrate metabolism develops, it becomes increasingly apparent that the liver is particularly important in its regulation. This fact is brought to the fore in hepatic diseases, especially in cirrhosis. It is with this phase that we are concerned in our present study of 19 cases of cirrhosis, 3 of which were associated with cardiac failure, and of 10 cases of infectious hepatitis in various stages of convalescence.

The diagnosis in all cases of cirrhosis was proven not only by the clinical and laboratory manifestations, but also by liver biopsy obtained with the Vim-Silverman needle. There were no complications with this latter procedure. It is not our purpose to consider the pathogenesis nor the clinical manifestations of liver disease, but rather to investigate the ability of patients with hepatic disease to handle glucose as demonstrated by the alteration of the 3 common types of glucose tolerance tests in present use, *i.e.*, the one-dose oral ("standard"), the one-hour, 2-dose oral (Exton-Rose) and the intravenous. We have attempted to ascertain which of these tests is most significant as an index of liver function in so far as carbohydrate metabolism is concerned and how it correlates with the clinical picture and with other liver function tests as an index of liver disease.

Observations. An evaluation of the patients, at the time of the present study, revealed that the general condition and prognosis of the 19 cases of cirrhosis was good in 6, fair in 4, and poor in 9. The ages ranged between 32 and 68 with an average age of 49 years. Thirteen of the 19 patients had a history of chronic alcoholism. The duration of symptoms ranged between 3 months and 11 years (average 2 years and 3 months). The most frequent complaints were abdominal discomfort (13 cases), weight loss (9 cases), jaundice (8 cases), shortness of breath (8 cases), weakness (7 cases), nervousness (6 cases), loss of appetite (6 cases), vomiting (5 cases), swelling of ankles (4 cases), cough (2 cases), and vomiting of blood (2 cases).

Hepatomegaly of a considerable degree was a prominent feature in the cases with cirrhosis which included those with far advanced disease and a poor prognosis. This finding is in contrast to the small liver described in the literature as being typical of advanced cirrhosis. Hepatic enlargement was termed minimal when the liver edge was palpable 2 to 3 cm., moder-

ate when 3 to 8 cm. and marked when over 8 cm. below the costal margin. Thus, according to these criteria, the hepatomegaly was marked in 10 of the cases of cirrhosis, moderate in 7, and minimal in 2.

The remaining clinical manifestations show fairly good correlation with those found in a similar series.[13] Spider angiomata were noted in 10 cases, ascites was noted in 7 cases, peripheral edema in 7 cases, and splenomegaly in 4 cases.

The patients with hepatitis were in various stages of convalescence. The prognosis and general condition was good in all. The duration of symptoms ranged between 4 weeks and 2 years (average 5 months). The average age, being 30, was considerably lower than that of the patients with cirrhosis. The most frequent complaints were jaundice (seen in all patients and recurrent in 5), nausea, anorexia, low grade fever, right upper quadrant tenderness, and neurasthenic symptoms following the acute illness. Hepatomegaly was seen in 7 of the 10 cases initially and was present in 3 at the time of this study.

The results of certain liver function tests, other than glucose tolerance, performed on the patients are summarized in Table 1.

Although jaundice usually has not been considered a manifestation of cirrhosis,[39,41] 8 of the 19 cases, or about one-half had a definite history of jaundice. Moreover, 8 cases, 4 of whom had a history of jaundice, showed an elevation of the icteric index, at the time of this study, from minimal to moderate in amount, (Table 1). Foley *et al.*[9] reported elevated icteric indices in 20 of 21 cases of cirrhosis.

TABLE 1. LIVER FUNCTION STUDIES

Case No.	**BSP Retent.*	*Icterus Index*	*Ceph.Floc. 24 hrs.*	*Ceph.Floc. 48 hrs.*	*Thymol. Turb.*	*Proth. Time Pats.*	*Proth. Time Control*	*A/G Ratio*		*RBC*	*Liver Biopsy*
1	14%	16	—	—	—	—	—	3.5/3.0	3.3	Mil.	Cirrhosis
2	5%	8	0	0	—	—	—	3.5/2.8	4.0	Mil.	Cirrhosis
3	12%	24	0	1+	0	10	15	4.0/2.3	4.0	Mil.	Cirrhosis
4	14%	12	0	1+	9.5	26	15	3.4/3.2	3.3	Mil.	Cirrhosis
5	17%	8	0	0	2	14	16	5.1/3.1	3.9	Mil.	Cirrhosis
6	18%	10	1+	2+	4	14	17	3.0/2.8	4.1	Mil.	Cirrhosis
7	18%	27	1+	2+	9.5	27	15	3.8/4.0	3.8	Mil.	Cirrhosis
8	26%	42	2+	3+	15	24	17	2.1/4.2	4.1	Mil.	Cirrhosis
9	29%	2	0	0	3.5	9	15	5.5/1.9	4.5	Mil.	Cirrhosis
10	35%	12	0	0	0	13	18	3.2/2.5	4.15	Mil.	Cirrhosis
11	22%	10	0	1+	—	18	14	3.9/4.1	2.2	Mil.	Cirrhosis
12	10%	6	0	0	1	15	17	4.6/2.5	4.6	Mil.	Cirrhosis
13	3%	8	0	0	—	41	18	4.0/2.7	3.5	Mil.	Cirrhosis
14	10%	6	0	0	—	15	19	3.1/2.8	3.0	Mil.	Cirrhosis
15	14%	20	0	0	—	23	17	4.0/3.0	3.2	Mil.	Cirrhosis
16	34%	29	0	1+	2.5	21	16	4.0/3.7	4.2	Mil.	Cirrhosis
17	11%	8	0	1+	5	17	16	—	4.4	Mil.	Cirrhosis
18	29%	4	Neg	3+	4	15	17	4.4/2.3	4.2	Mil.	Cirrhosis
19	30%	5	0	0	3	—	—	4.1/1.2	3.8	Mil.	Cirrhosis
20	14%	24	—	—	5	15	15	4.3/3.4	4.2	Mil	Hepatitis
21	7%	6	0	0	2	14	15	4.3/2.4	4.6	Mil.	Hepatitis
22	9%	4	0	0	9	19	16	4.1/2.4	5.0	Mil.	Hepatitis
23	1%	5	0	0	0	14	18	4.1/3.4	4.3	Mil.	Hepatitis
24	2%	4	0	0	0	17	18	4.4/2.8	4.5	Mil.	Hepatitis
25	3%	12	0	0	0	15	18	4.0/3.0	4.4	Mil.	Hepatitis
26	10%	18	—	—	—	20	16	4.1/2.9	4.5	Mil.	Hepatitis
27	20%	16	0	1+	3	16	18	5.9/3.2	4.1	Mil.	Hepatitis
28	41%	24	0	1+	16	17	18	5.0/2.5	5.4	Mil.	Hepatitis
29	1%	17	0	0	0	—	—	—	4.5	Mil.	Hepatitis

* Determinations done 45 minutes after 5 mg. of dye per kg. of body weight was injected. Over 5% retention was regarded as abnormal by this laboratory.

The normal cephalin flocculation studies in such a high percentage of the cases may be due to the laboratory technique of this hospital since the very small number of patients with liver disease showing disturbances of this test has been noted by us previously.

Low serum albumin and anemia of some degree were the rule rather than the exception. This has been noted by others.[13]

The results of the 3 glucose tolerance tests as well as the post prandial blood sugar level have been tabulated for each patient in Table 2. The post prandial blood sugar was ascertained 2½ hours after the patient had been given a standard meal of 100 grams of carbohydrate, 35 grams of fat, and 35 grams of protein. The blood sugar estimations were obtained from venous blood after the method of Folin and Wu.[10]

TABLE 2. TABULATION OF BLOOD SUGAR LEVELS DURING 3 TYPES OF GLUCOSE TOLERANCE TESTS

Case	Diagnosis	*Standard Oral Test*					*Exton-Rose*			*Intravenous Test*					*P.P.*
		F.	*½Hr*	*1Hr*	*2Hr*	*3Hr*	*F.*	*½Hr*	*1Hr*	*F.*	*½Hr*	*1Hr*	*2Hr*	*3Hr*	
1	Cirrhosis	123	215	260	180	85	129	245	273	145	396	252	200	115	200
2	Cirrhosis	93	200	249	176	100	114	176	188	115	299	230	110	68	100
3	Cirrhosis	95	171	188	171	91	113	168	256	105	281	195	133	91	123
4	Cirrhosis	108	195	256	219	105	98	170	209	108	286	267	162	105	—
5	Cirrhosis	109	170	209	127	81	80	109	144	102	256	122	87	87	112
6	Cirrhosis	112	130	192	157	68	94	143	208	87	238	174	152	70	108
7	Cirrhosis	118	195	240	181	90	110	267	162	111	217	132	93	137	100
8	Cirrhosis	186	200	286	290	200	157	195	229	109	276	238	138	110	205
9	Cirrhosis	84	150	141	142	77	92	150	170	100	291	191	119	91	81
10	Cirrhosis	96	180	167	130	122	82	105	113	90	250	135	95	95	105
11	Cirrhosis	146	342	420	512	510	155	250	340	128	460	359	273	181	—
12	Cirrhosis	147	226	300	217	203	159	256	264	143	300	224	176	132	—
13	Cirrhosis	93	158	129	120	79	102	172	167	99	238	121	83	83	—
14	Cirrhosis	110	186	240	77	70	91	127	156	120	360	215	109	81	114
15	Cirrhosis	98	135	139	95	58	111	178	206	90	245	130	78	75	123
16	Cirrhosis	102	160	128	102	90	98	132	160	100	200	196	105	100	99
17	Cirrhosis	57	158	117	60	57	68	196	191	76	214	146	84	76	109
18	Cirrhosis	118	190	182	162	162	98	170	209	79	288	158	137	129	123
19	Cirrhosis	100	132	139	120	74	87	119	135	78	169	113	78	82	104
20	Hepatitis	76	114	191	162	143	100	165	261	91	214	176	91	100	113
21	Hepatitis	76	114	133	114	76	66	96	150	68	204	141	91	87	96
22	Hepatitis	104	122	128	113	96	113	149	133	109	200	105	96	109	79
23	Hepatitis	81	162	100	81	81	79	152	157	93	338	129	81	92	157
24	Hepatitis	117	156	139	117	111	104	138	135	95	280	135	65	90	76
25	Hepatitis	88	136	105	92	81	78	120	135	92	254	97	94	88	—
26	Hepatitis	102	241	219	118	118	105	192	196	103	244	169	115	96	150
27	Hepatitis	81	132	123	113	109	110	140	130	102	353	211	116	106	100
28	Hepatitis	91	121	227	87	71	83	120	145	85	170	105	100	95	110
29	Hepatitis	88	122	117	62	70	100	127	122	104	205	104	100	86	81
MEAN		103	172	185	148	113	103	164	184	101	264	171	116	98	—
Standard Deviation		25	47	73	85	83	23	44	54	17	66	59	42	23	—
Mean of 103 Normal Controls[29]		96	145	128	95	82	97	138	131	96	223	126	88	91	98
Standard Deviation for Controls		11	25	30	15	16	10	25	34	11	69	41	13	13	18

The standard deviation was calculated by use of the following formula:

$$\text{St.D.} = \sqrt{\frac{\Sigma x^2}{N} - M^2} \qquad M = \text{means}$$

Calculations made by Department of Biometrics, Randolph Army Air Field, Texas.

Each patient was placed on a diet of 280 grams of carbohydrate, 100 grams of protein, and 100 grams of fat for at least 5 days before any glucose tolerance tests were done in order to eliminate discrepancies due to dietary influences. Two days or more were allowed between tests.

Techniques: The standard glucose tolerance test was made by obtaining the blood sugar level in the morning, after 12 hours fasting, and again ½ hour, 1 hour, 2 hours, and 3 hours following the ingestion of 100 gm. of glucose dissolved in 600 cc. of water flavored with lemon juice.

The one-hour, 2-dose Exton-Rose test was done, by dissolving 100 gm. of glucose in 600 cc. of water and flavoring with lemon juice. A fasting blood sugar was then taken, following which half of the glucose (50 gm.) was given by mouth. A second blood sugar was taken after 30 minutes following which the remaining 50 gm. of glucose was ingested. A third blood sugar was then taken ½ hour later.

The intravenous glucose tolerance test was done by administering 0.5 gm. of glucose per kg. of ideal weight, in 300 cc. of normal saline. The glucose was given by intravenous drip over a minimum of 20 and a maximum of 30 minutes. Blood specimens were obtained in the fasting state and ½ hour, 1 hour, 2 hours, and 3 hours after the intravenous drip was started.

Table 3 shows an analysis and comparison of the number of cases showing decreased glucose tolerance in one or more of the 3 tests according to the criteria of various authors for interpretation of normality versus abnormality. Referring to Table 2, we note that in Cases 7 and 16 the 1-hour blood sugar values in the Exton-Rose test are 162 and 160 mg. per 100 cc. respectively. These, because of the small deviation, will be regarded as within normal limits according to the criteria of Mathews *et al.* (below 158 mg. (item 3, Table 3)), since in the opinion of the authors such a sharp line of distinction does not exist. Under the same token, in Case 27, the 2 hour blood sugar level of 116 mg. per 100 cc. for the intravenous test, (criterion 5, Table 3), will be considered within normal range.

In an evaluation of the standard glucose tolerance test in these patients the maximum blood sugar, or "rise," was not taken to be indicative of abnormality since this value is too dependent on extra-metabolic factors such as gastro-intestinal absorption, etc. Joslin[19] states that a rise above 170 mg. per 100 cc. is abnormal. However, in the authors' experience,[29] and that of others, the maximum blood sugar concentration may be considerably more than 170 mg. in normal individuals. For example, in a series of 103 normal young male controls, 16 (15%) were found to have maximum blood sugar levels during the first hour of the standard test well in excess of 170 mg.[29] When the mean value plus or minus twice the standard deviation was used for determining the range of blood sugar, it was found to be 95 to 195 mg. for the 30 minute sample, and 68 to 188 mg. for the one hour sample, as compared to 65 to 125 mg. by the second hour. Standard deviation values of 25 for the ½-hour, 30 for the 1-hour, as compared to 15 at 2 hours, likewise attest to a wide range of normality during the first hour.

The criterion of Gould *et al.*,[14] for the standard test, *i.e.*, 3 hour blood sugar below the fasting level, is included in Table 3 for comparison. This criterion, also apparent in the small series of liver disease, is of value in estimating the severity of disturbance of carbohydrate metabolism as shown by the authors elsewhere[29]; but is too insensitive as an absolute criterion, and for that reason will not be included further in this discussion.

The criteria for a normal standard tolerance test, as outlined by the authors (item 7, Table 3), so nearly parallel those of others,[8,11,12,15,16] as outlined in item 1, Table 3, that the latter will be used in further discussion, *i.e.*, fasting and 2-hour blood sugar below 120 mg. per 100 cc.

In comparison of the 3 tests the criteria used for a normal intravenous test are those found by the authors on 103 controls[29] *i.e.*, normal fasting blood sugar and 2 hour value below 115 mg. (Table 3). However, these same values were arrived at by Lozner and associates[23] who found the normal range of the 2 hour blood sugar to be up to 90 mg. In their blood analysis, however, they used the Somogyi zinc precipitation method which determines fermentable "true sugar" levels. These average 10 to 30 mg. below the levels found by Folin-Wu tungstate precipitation[19] used by the authors. Using the latter analytic technique in their studies, Lozner *et al.*[23] could expect the 2-hour blood sugar to range up to 115 mg. per 100 cc.

In evaluating the 1-hour, 2-dose test in this series of cases, the criteria of Matthews and coworkers (criterion 3, Table 3)[26] were used. According to these authors, they are more specific than the criteria of Exton and Rose (criterion 4, Table 3)[8] thus resulting in fewer false positives. Our viewpoint, developed as a result of comparative tests run on 103 normal subjects,[29] coincides. Duncan further states in his book *Metabolic Diseases* that the criteria of Matthews *et al.* are the most widely accepted today where the 1-hour, 2-dose test is used. This conclusion is supported by Table 3 in which 22 cases show abnormalities according to the criteria of Exton and Rose as compared to 15 cases by the criteria of Matthews and associates and 14 cases when the standard test is used for evaluation.

TABLE 3. COMPARISON OF ABNORMAL RESULTS ON THREE TYPES OF GLUCOSE TOLERANCE TESTS DEPENDING ON CRITERIA USED

CRITERIA	*19 CASES CIRRHOSIS*	*10 CASES CONV. HEPATITIS*	*TOTAL*
**1. No. of cases with fasting or 2 hr. blood sugar above 120 mg. per 100 cc. on the standard oral test.[8, 11, 12, 15, 16]	13	1	14
2. No. of cases with 3 hr. blood sugar above the fasting level on the standard oral test. Gould *et al.*[14]	6	3	9
**3. No. of cases with abnormal fasting blood sugars or 1 hr. blood sugars above 158 mg. per 100 cc. on the Exton-Rose test. Mathews *et al.*[26]	13	2	15
4. No. of cases with abnormal Exton-Rose tests according to criteria of Exton and Rose.[8]*	17	5	22
**5. No. of cases with abnormal fasting or 2 hr. blood sugars above 115 mg. per cc. on the I.V. test.[23, 29]	9	0	9
6. No. of cases with abnormal curves according to criteria of both #1 and #3.	10	1	11
7. No. of cases with abnormal standard curves according to authors' criteria of normal obtained on 103 controls[29] *i.e.*, fasting blood sugar below 120 mg. per cc. and 2 hr. blood sugar below 125 mg. per cc.***	13	1	14

* Criteria of Exton and Rose for normal individuals are as follows:
1. Normal fasting blood sugar
2. Rise in blood sugar of not more than 75 mg. per 100 cc. at ½ hour.
3. I hour sample not to exceed the ½ hour specimen by more than 5 mg.

** Criteria used for interpretation of each test and for comparison of the three types of glucose tolerance tests, referred to in the discussion.

*** Conclusion reached by using the mean value (95.0 mg. for the 2 hour value) ± twice the standard deviation (15.0)

Therefore, in further discussion and comparison of the 3 types of glucose tolerance tests, the criterion of item 1, Table 3, will be used for the standard 1-dose test; the criteria of Matthews *et al.* (item 3, Table 3) for the one-hour, 2-dose test, and the criteria of item 5, Table 3, for the intravenous test. The cases showing discrepancies between the 3 types of tests according to these criteria are tabulated in Table 4 along with the critical discrepancy values.

as having a definitely abnormal standard tolerance test with a normal Exton-Rose test. On the other hand, 4 (Cases 13, 15, 17, and 26 (Table 4)) had abnormal Exton-Rose tests with normal standard tests.

The intravenous test was within normal limits in all (Cases 5, 7, 10, 13, 15, 17, and 26), showing discrepancies between the standard and the Exton-Rose tests, and therefore was of little aid in evaluation of these discrepancies.

TABLE 4. CASES SHOWING DISCREPANCIES BETWEEN THREE GLUCOSE TOLERANCE TESTS EMPLOYED

CASE NO.	*2 hr. BLOOD SUGAR STAND. TEST*	*1 hr. BLOOD SUGAR EXTON-ROSE TEST*	*2 hr. BLOOD SUGAR I.V. TEST*
* 5	127 (Borderline)	144	87
* 7	181	162 (Considered normal)	93
*10	130 (Borderline)	113	95
**13	120	167	83
**15	95	206	109
**17	60	191	84
**26	118	196	115
*** 2	176	188	110
***20	162	261	91

* Abnormal standard test because of a 2-hour blood sugar above 120 mg. per 100 cc. (item 1, Table 3) with normal 1-hour, 2-dose tests according to criteria of Matthews *et al.* and normal intravenous tests.
** Abnormal 1 hour, 2 dose test with normal standard test, and normal intravenous test.
*** Abnormal 1 hour, 2 dose and standard tests with normal intravenous tests.

In the entire series of 29 patients, 9 had abnormal intravenous, one-hour, 2-dose, and standard tests. These, all of whom had cirrhosis, were the only patients showing abnormalities of the intravenous test. In addition, 9 patients showed discrepancies (Table 4) between the 3 tests. Thus, 2 patients (cases 2 and 20) had both abnormal one-hour, 2-dose and standard tests with a normal intravenous test. Three cases had abnormal standard tests and normal Exton-Rose tests. Two of these (Cases 5 and 10, Table 4) had 2-hour blood sugars of 127 and 130 mg. respectively on the standard test. These would be classified as borderline or presumptively diabetic. Therefore, only one (Case 7) would be classed

Because of reports in the literature[6] of the marked hypoglycemia in liver disease, particularly in the fasting state, this problem was studied further since our results did not seem to bear out this observation. Three cases of cirrhosis not included in this series of 29 were selected for 12 hour glucose tolerance tests to evaluate the fluctuation of blood sugar over a more prolonged period of time. The standard test was chosen since, in our experience, it seemed to be the most valid. The results are tabulated in Table 5.

Discussion. In the glucose tolerance tests in this series, it is apparent that the ability of patients with liver disease to handle glucose is altered in a high percentage of the cases regardless

of the type of test or criteria for abnormality used.

What part does the liver play in the normal glucose tolerance test?

The importance of hepatic glycogen storage seems well substantiated. Pachman[30] has found experimentally a substantial increase of liver glycogen following the oral test, but feels that this is not the only factor operative since tissue storage and utilization are also important. Moreover, Ravdin *et al.*[33] report that if the diet is deficient in carbohydrate, the liver becomes depleted of glycogen.

Employing the intravenous infusion of glucose, Sosken *et al.*[36] in determining the amount of glucose entering and leaving the liver, found that it was stored in significant amounts during the first 2 hours. However, they did not determine the form in which it was stored. Thirty minutes after the intravenous administration of glucose, Palmer[31] was unable to find an increase of glucose in the liver. Ravdin further found that liver glycogen could be increased 84% by the administration of intravenous glucose, or 236% when forced feeding plus intravenous glucose was employed. In drawing conclusions from these results, the presumptive evidence is that a large part of the glucose taken orally or intravenously is metabolized in the liver as a storage product, glycogen or a closely allied compound. In addition, the tissue metabolic factor may play a considerable role.[6] McKean[28] further points out that a large factor in the sudden drop in blood glucose after the intravenous administration is due merely to diffusion into the tissues. Urinary excretion is apparently not an important factor since Pachman[30] found not more than 2 gm. to be excreted during the intravenous test in normal adults. There also is no change in respiratory quotient nor in basal metabolic rate to indicate increased oxidation.[6,30]

If the exact fate of administered glucose in the body is controversial, the regulation of this fate is even more so, particularly the role of hepatic function. Sweeney[38] concluded that the configuration of the normal glucose tolerance curve is due to increased secretion of insulin as a result of pancreatic stimulation following the administration of glucose, resulting in the rapid storage of glucose and a drop in blood sugar ensuing. The hypoglycemic phase was thought to be due to the over secretion of insulin.

In contrast, Soskin, Allweiss, and Cohn[36] obtained normal dextrose tolerance curves with the usual hypoglycemic phases in depancreatized animals which, before and during the experiment, were given a constant infusion of insulin and glucose in amounts which would maintain normal blood sugar levels in the fasting state. They concluded that the liver and its homeostatic mechanism was the all important factor in the rise and fall pattern of the normal glucose tolerance curve and not the variation in insulin liberation by the pancreas. They further found that if enough liver was removed to cause hepatic insufficiency, any degree of diabetic glucose tolerance curve could be produced depend-

TABLE 5. BLOOD SUGAR VALUES OVER A 12 HOUR PERIOD AFTER THE INGESTION OF 100 GRAMS OF GLUCOSE

Case	*F.*	*½h.*	*1h.*	*2h.*	*3h.*	*4h.*	*6h.*	*8h.*	*10h.*	*12h.*
30	123	180	200	175	140	120	61	111	90	115
31	90	190	148	130	100	90	100	110	75	84
32	64	164	130	100	65	70	75	70	74	60

ing on the amount of insufficiency produced.

Further, emphasizing the importance of the liver factor in the regulation of blood sugar levels is the work of Mann and Bollman.[25] They found that a partially hepatectomized animal would not die from hypoglycemia, but that glucose tolerance was impaired, resulting in a diabetic type curve; whereas completely hepatectomized animals rapidly died of hypoglycemic shock even though the muscle glycogen content was normal. This latter finding, according to Peters and Van Slyke,[32] is due to inadequate phosphatase in the peripheral tissue to catalyze the phosphorylation and break down of the muscle glycogen into glucose for liberation into the blood stream.

Lewis and Izume[21] have shown experimentally that in animals with liver damage produced by hydrazine there is also a resultant failure of glycogen storage in the liver after a standard dose of glucose, resulting in a diabetic type of glucose tolerance curve. However, after a prolonged time these same animals developed a marked hypoglycemia. This observation was substantiated by McIntosh[27] in studies on animals with liver damage due to other hepatotoxic substances. Thus, there is failure on the part of the liver to remove dextrose from the blood when the sugar content is high and a failure to maintain normal levels when low; i.e., the homeostatic mechanism was severely disturbed. Lewis and Izume also found impaired conversion of amino acids into glucose. Conn *et al.*[6] minimized this factor in patients on an adequate diet. Other observers [4,6,42] have found glucose tolerance to be altered in infectious hepatitis as well as in liver damage secondary to burns.[44] Therefore, it seems well established that the presence of an adequate amount of properly functioning liver tissue is necessary for the control of carbohydrate metabolism which depends on the balance between glycogenesis, glycogenolysis, and glyconeogenesis.

How may these findings be applied clinically to the understanding and evaluation of chronic liver disease?

Soskin[35] reported abnormal glucose tolerance in chronic liver diseases and suggested that glucose tolerance be used as a liver function test. Jacobi[17] has gone so far as to attempt to differentiate intrinsic liver disease from the extrinsic forms such as carcinoma and common duct obstruction. According to his observations, glucose tolerance is decreased in both types of disease; but in the intrinsic type of pathological changes, he found a continued rise in blood sugar after 3 to 4 hours when employing the oral standard one-dose test, while in the extrinsic liver disease, the curve is abnormally elevated, but tends to fall gradually. On the other hand, Wilson[42] has observed that extrinsic disease such as chronic, passive congestion and obstructive jaundice do not appear to alter glucose tolerance. Pachman[30] has further concluded that dextrose tolerance is not a satisfactory aid in the differential diagnosis of jaundice.

If one notes in Table 2 the marked variation of glucose tolerance in this series of patients with intrinsic liver disease, this latter conclusion of Pachman seems justified. The degree of impairment will depend on the amount of hepato-cellular damage and resultant functioning reserve, rather than the etiological background. Since in extrinsic liver disease the hepatocellular damage is at a minimum, in comparison to the damage present in intrinsic liver disease, less impairment of hepatic function would be expected in the former instance. However, the degree

of hepato-cellular damage in intrinsic liver disease is so variable, resulting in such notable variation of glucose tolerance as seen in Table 2, that it is understandable why this test would not aid in the differential diagnosis of jaundice. One might also note, as Pachman[30] has already done in his study, that there is apparently no correlation between the degree of icterus and the severity of glucose tolerance impairment in this series.

In addition Pachman[30] has concluded that dextrose tolerance is not a reliable procedure for indicating impaired hepatic function. This seems unjustified to us in view of our findings in this series, as well as the findings of others[3,6,28,42] who found the dextrose tolerance test to be a good index of hepatic function, although not a constant one, which compares quite well with other well known liver function tests.

It is granted, as noted by Mann[24] and Tunbridge and Allibone,[40] that glucose tolerance depends on many extra-hepatic factors; and that glucose tolerance alteration is not specific for any disease, since it has been noted to be abnormal in such varied pathological states as diabetes, hyperthyroidism, nephritis, rickets, obesity, arteriosclerosis, cancer, pituitary disorders, arthritis, etc.[2,7,18,45] However, if these facts are recognized and the patient is evaluated with this in mind, with proper dietary standardization before the test, it appears to us that glucose tolerance testing may afford considerable aid in evaluation of hepatic function. In Table 3, it is evident that in the 19 patients with cirrhosis, regardless of the criteria or type of test used, the incidence of impaired glucose tolerance compares quite favorably with the results of other liver function tests, (Table 1). This seems particularly pertinent to us, since glucose tolerance testing involves the evaluation of a physiological process that normally takes place in the liver. Disturbance of glucose tolerance was not a notable finding in the patients convalescing from hepatitis.

Conn *et al.*,[6] attempting to evaluate glucose tolerance in chronic liver disease, have concluded that impaired carbohydrate utilization was one of rate rather than of total disability, since the blood sugar usually returns to normal in 4 to 5 hours. They found no explanation for the delay other than impaired glycogenesis since there was no change of basal metabolic rate or respiratory quotient to indicate change of metabolite or increase in the rate at which it was being utilized.

These workers have also noted in their studies that a fasting hypoglycemia was an outstanding and constant finding, apparently on the basis of decreased glycogenolysis, possibly a result of decreased glycogen storage. In referring to Table 2, one notes that this finding has not been duplicated in our series of patients. In an attempt to investigate further this factor, three 12-hour oral tolerance tests were done.

In Table 5 one notices the marked fluctuation of blood sugar over a 12 hour period after the ingestion of 100 gm. of glucose. This would seem to indicate instability of carbohydrate metabolic regulation or failure of the homeostatic mechanism of the liver. However, consistent hypoglycemia was not in evidence.

Jacobi[17] has noted other characteristics of the glucose tolerance curve in liver disease. In his study of 25 cases, the oral glucose tolerance test was flat, or had a high rise with a fall to normal within 2 hours. In contrast, Wilson[42] found that the curves of advanced cirrhosis were characterized by a low peak, a sudden initial drop, and a very delayed return to fasting level with

little if any change in cases of mild hepatic insufficiency.

However, when one critically examines Table 2, it becomes apparent that in this series there is no completely typical curve. Some curves are "diabetic," others are normal, while others are flat, and a few have a high peak with a sudden drop. The most common abnormality is the "diabetic type" curve which in some cases may continue to rise even after 3 hours. The curves in these cases apparently differ in no way from those found in mild to moderately severe "true pancreatic diabetes." One would ordinarily conclude from the fasting blood sugars and grossly abnormal curves that Cases 8, 11, and 12 had an absolute insulin deficiency as well as hepatic deficiency. In view of the complete evaluation of these patients as to age of onset, clinical picture and laboratory studies, it is the opinion of the authors that this was not so, but absolute proof to the contrary is lacking. None of the patients included in this series received insulin during their course of therapy despite the apparently severe disturbance of carbohydrate metabolic regulation. It should be kept in mind that the diagnosis in this series of cases was made not only on clinical grounds, but was confirmed by pathological examination of liver tissue.

What is the most practical and valuable type of glucose tolerance test to use as a liver function study?

By reference to Table 2 we see that post prandial blood sugars are only a crude method of evaluation of carbohydrate metabolism and a poor index of hepatic function.

Wilson,[42] using an intravenous test on a series of patients with chronic hepatoses, found a significant number of cases with decreased tolerance by comparison to a control series. However, Pachman[30] thinks that the oral test is more significant and more physiological than the intravenous test. In his series, when the intravenous test was abnormal, the oral test was always abnormal, but frequently the oral test was abnormal and the intravenous test normal. This same fact is outstanding in the series being reviewed at present. In Table 3, it is evident that in 9 patients the intravenous test was abnormal according to the criteria used (item 5). The standard and the one-hour oral tests (using the criteria of Matthews *et al.*) were also abnormal in all these cases. In addition, 6 patients had abnormal standard tests (2 of which were borderline only (Table 4)), and 7 had abnormal one-hour, 2-dose tests. One should also note a tendency to blood sugar depression in the 3 hour specimen of the intravenous test as compared to the same time interval in the standard oral test, although the maximum blood sugar level was much greater in the former. It would appear that the intravenous test is less sensitive to minor alterations of glucose tolerance and should be reserved for occasions when the oral method is impractical or when evaluation of gastro-intestinal absorption is a factor.

Evaluation of the standard test versus the one-hour, 2-dose test is more difficult. In reviewing Tables 2 and 3 one is immediately impressed by the number of cases showing decreased glucose tolerance when the oral test is used, regardless of which test is used and which criteria are employed for interpretation. Of the 19 cases of cirrhosis and 10 of convalescent hepatitis, 13 and 1 respectively showed abnormal standard curves. When the criteria of Matthews *et al.* are used for interpretation of the one-hour, 2-dose test, 13 patients with cirrhosis and 2 cases of convalescent hepatitis revealed decreased tolerance, 11 of which were also included in the above group with

abnormal standard tests. Of these 11 patients with both abnormal standard and one-hour, 2-dose tests, 9 also had abnormal intravenous tests as noted above, and 2 had normal intravenous tests. In addition to these 11 patients, if we refer to Table 4, we find 2 patients with borderline standard tests who had normal one-hour, 2-dose tests. Only one patient had a definitely abnormal standard test, with a normal one-hour, 2-dose test. On the other hand, 4 patients had abnormal one-hour oral tests with normal standard tests. Thus, although the series is definitely too small for significant statistical analysis, if we accept the standard test as a point of reference for comparison, these results would seem to indicate that the one-hour, 2-dose test is either too variable, or the existing criteria for interpretation are too rigid so that the accuracy of this test cannot be accepted as valid. Therefore, the standard oral test remains the most valid approach to the determination of glucose tolerance. This conclusion bears out a similar observation made by the authors on 103 control cases.[29]

Conclusions. 1. Carbohydrate metabolism is disturbed in chronic liver disease, resulting in decreased glucose tolerance.

2. The glucose tolerance test obtained following a standardized dietary preparation is a satisfactory method to aid in the evaluation of liver function and compares quite favorably with other methods in present use, having the advantage of being a physiological evaluation.

3. Although the standard, one-dose test and the one-hour, 2-dose test are somewhat comparable, the standard test is apparently the more valid in determining abnormalities of glucose tolerance. The intravenous test is inferior to the oral glucose tolerance test as an index of hepatic function and only under special circumstances is it of use as an adjunct to the oral test methods.

4. If a minimum of venipunctures is desired, the fasting and the 2-hour blood sugars, otherwise employing the technique of the standard test, would appear to be most valid.

5. The most efficacious procedure in drawing definite diagnostic conclusions of hepato-cellular pathology is the liver biopsy.

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THE VISCERAL MANIFESTATIONS OF SCLERODERMA A REVIEW OF THE RECENT LITERATURE

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Visceral manifestations of scleroderma have been recognized for more than 50 years, but little attention has been paid to them in discussions of this disease either in dermatological or in general medical texts. Perhaps much of this relative inattention may be due to the infrequent occurrence of scleroderma but undoubtedly some of it is the result of general lack of appreciation of the multitudinous visceral manifestations such patients may present. Furthermore, it is assumed that the development of symptoms referable to one or another internal organ of a patient suffering from scleroderma does not necessarily imply that the lesion of the affected organ is sclerodermatous in nature, especially if there is little cutaneous involvement. Therefore, because detailing of the internal manifestations of generalized scleroderma may stimulate the internist to be on the lookout for cutaneous lesions of this process and alert the dermatologist to the possibility of associated internal lesions, we propose to survey some of the recent literature dealing with these visceral complications of diffuse scleroderma.

The systemic character of scleroderma is suggested by the definition of this disorder given by Becker and Obermayer[5] which is a modification of that proposed by Ehrmann and Brünauer:[16] "Generalized scleroderma is not strictly a dermatosis, but rather a disease of the connective tissue of various organs and systems, the skin, subcutaneous tissues, the muscles, bones and joints, tendons and fascias, the serous surface, internal organs, endocrine glands and nervous system. The patient first notes the surface alterations, consequently the dermatologist is usually first consulted."

The variety and types of lesions found in scleroderma in the past are indicated by the findings in autopsies.[16]

The muscles show increased connec-

tive tissue, histologically (interstitial myositis). The muscle vessels show severe changes, even to localized arterial obliteration, proliferation of the media as well as thickening and round cell infiltration of the adventitia. The capillaries often appear like long solid cellular strands. The veins show only endothelial proliferation. The muscle bundles are secondarily altered and show vacuoles as well as signs of atrophy. Changes in the bones include fusions of the periosteum with the surrounding soft parts; the periosteum may be easily stripped or be bound down by young fibrous tissue. There are also changes in the bone cortex and marrow. The marrow may be aplastic so that hematopoietic tissue may regenerate in the spleen and enlarge it. The splenic blood vessels are also severely damaged. Similar changes occur in joints. All studies of the internal organs show the same features—edematous infiltration, cellular infiltration and proliferation of the connective tissue which is followed by atrophic changes in the parenchyma. Blood vessels of all types are badly damaged. In the older literature there are references to affection of the heart (endocardium, valves, pericardium and myocardium), lungs (increase in interalveolar connective tissue and severely damaged blood vessels); liver, kidneys and spleen, lymphatic vessel system (occlusion of ductus thoracicus as well as nodular formations in the lymphatics); thyroid gland (atrophy or gross changes, but microscopically demonstrable connective tissue increase, and blood vessel injury); nervous system, peripheral and central (neuritis and degenerative changes, increase in connective tissue and thickening of the nerve sheaths in peripheral nerves and various proliferative and degenerative changes in the central nervous system). Ears and eyes have also been involved. The latter may show bilateral cataract as well as less serious involvement.

The recent excellent study of Goetz[21] shows the great variety of lesions a single patient may present. He found for example, that his patient had the following sclerodermatous changes: Raynaud's phenomenon and pin point ulcers in various digits; on the skin, scleroderma; telangiectasia and calcinosis; gastrointestinal complaints, dysphagia and symptoms referable to esophageal ulcer, with radiologic demonstration of dilatation of middle third and narrowing of lower third of the esophagus, esophageal ulceration, lack of peristalsis and stasis in the duodenum, small and large bowel, with dilatation of individual loops of small bowel and extreme narrowing of part of the large bowel (findings were confirmed at autopsy); atrophy and fibrosis of muscles, extensive myocardial fibrosis of unusual type which had given various clinical evidences of heart involvement; marked changes in the kidneys, liver, spleen and lungs; and constitutional and hormonal disturbances; that is, marked loss of weight, pigmentation, loss of axillary and pubic hair and amenorrhea.

In passing it may be noted that if the infectious cause of scleroderma as claimed by Wuerthele-Caspe, Brodkin and Mermod[82] were established, the development of widespread lesions would be easy to understand. Furthermore, it may be stated that the diffuse involvement of the collagen system, such as is also seen in disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa, need not imply a single cause for all these lesions though it strongly suggests a common pathogenetic denominator.[1,2,38a,b,60]

Let us now consider what is regarded by dermatologists as diffuse or generalized scleroderma from the clinical

standpoint and also its relation to acrosclerosis.

In most cases of diffuse scleroderma the process starts on the hands and feet with a somewhat later and slower involvement of the face. Three stages can be distinguished clinically: the edematous, the indurative and the atrophic stage. The initial edema does not pit on pressure. The skin appears tense and cannot be folded. The face assumes a mask-like expression; the regular folds smooth out. In the second phase the skin hardens and stiffens. This is particularly pronounced on the fingers, on the dorsa of the hands and in the region of the ankles. Hyperpigmented and depigmented spots appear in this stage. In the third stage the tips of the fingers become smaller and pointed, and the fingers are immobilized in a flexed position. The face, the nose, the ears, and the lips become gradually smaller and thinner. Ectropion develops, due to atrophy of the lids. All mucous membranes of the mouth (tongue, hard and soft palate and gums) may be involved in the indurative and atrophic process. Ulcers, probably due to tension and deficient circulation, develop mainly on the finger-tips, the elbows and the ankles.

For the purpose of this review we have assumed that scleroderma and acrosclerosis are the same disease, though Sellei,[68a,b,c,d] O'Leary[55] and others maintain that they are different.

In addition to the specific sources of information to be mentioned, special note should be made here of 3 important contributors to our present knowledge. The chapter in Jadassohn's Handbuch by Ehrmann and Brünauer is the summary of the lifetime effort of Ehrmann in this disease. Paul A. O'Leary of the Mayo Clinic has with his collaborators devoted more than 20 years to the furtherance of our knowledge of scleroderma, and allied diseases. Robert H. Goetz of the Department of Surgery, University of Cape Town and the Groote Schuur Hospital, Cape Town, has contributed a massive compilation of the knowledge of the visceral complications of this disease. Some of the views of these individuals are cited in extenso. No definite attempt is made to evaluate the various visceral manifestations from the standpoint of frequency of their occurrence or importance. Thus the extent of the discussion of a particular visceral manifestation in no way implies a special importance of that manifestation from the clinical or other aspect.

Pulmonary Lesions of Scleroderma. This subject has been reviewed recently by Dostrovsky[12] of Jerusalem, under the title of "Progressive Scleroderma of the Skin with Cystic Sclerodermal Changes of the Lungs." Previously pulmonary changes had been mentioned by Finlay,[18] von Notthafft,[53] Matsui,[48] Kraus[39] and Ehrmann and Brünauer[16] and Linenthal and Talkov.[46] More recently, references to pulmonary findings were made by Jackman,[33] Hale and Schatzki,[27] Weiss, Stead, Warren and Bailey,[76] Kanee,[35] Pugh, Kvale and Margulies[61] Goetz,[21] Getzowa,[20] Murphy Krainin and Gerson,[50] and Bevans.[6] Bevans points out that in one of her cases (Case 2) the anatomic lesions of the lungs were out of all proportion to the clinical and radiological findings. The vascular changes in the lungs were more extensive than those found elsewhere. In her other case (Case 1) the changes were slight and confined to the periphery of the lungs at the bases. She points out that although fibrosis of the lung is frequently described in general scleroderma, practically no mention is made of pulmonary insufficiency. Pugh and his associates believe that the pulmonary lesions of scleroderma have a

roentgenographic appearance which is distinctive though difficult to describe; their Figure 1 is labeled "Pulmonary fibrosis due to scleroderma."

In his detailed study, Dostrovsky[12] described peculiar pulmonary changes found in 3 cases of progressive scleroderma, reference to which had not been found in the literature. Because of pulmonary symptoms, 2 of the patients (Cases 1 and 3) were treated for tuberculosis. The roentgenograms showed peculiar changes of varying intensity, the correct interpretation of which was only made possible later by the autopsy findings. Getzowa[20] explained the formation of sclerotic cysts in the lungs as follows: "Disappearance of alveoli in the parenchyma and replacement by bronchiolar proliferation have taken place, the latter becoming progressively subject to cystic distention. The disappearance of alveoli is caused by a fibrous process of the alveolar walls, with subsequent dissolution."

Getzowa also described in addition to this "pulmosclerosis cystica," "pulmosclerosis compacta," consisting in disappearance of alveolar parenchyma as the result of progressive alveolar fibrosis without cyst formation. Dostrovsky believed that the pulmonary lesions were specific symptoms of the progressive sclerodermal syndrome and that both types, cystic sclerosis and fibrous solidification, are not rarities. They probably represent the final stage of pulmonary sclerosis.

Esophagus. Esophageal complaints in patients with generalized scleroderma are relatively frequent and often an early sign of the disease. Olsen, O'Leary and Kirklin in 1945[38] summarized the data on cases reported in the literature to that time as follows:

Their own experience, based on 350 cases of scleroderma and acrosclerosis, added 36 cases (approximately 10%). Their differentiation of diffuse scleroderma from scleroderma with Raynaud's syndrome (acrosclerosis), was thought to be unnecessary by Lindsay, Templeton and Rothman,[45] since acrosclerosis is, according to them, identical with diffuse or generalized scleroderma with sclerodactylia. As Olsen, O'Leary and Kirklin did not separate the two in their analysis of the literature, the present discussion will perforce follow their line since careful dermatologic differentiation is not always possible from the data submitted. From their own material, they were convinced that esophageal disturbances occur almost exclusively in cases of acrosclerosis rather than in those of generalized or diffuse scleroderma.

The first reference to esophageal complaints (dysphagia) in acute scleroderma was made by Ehrmann[15]

TABLE 1. SUMMARY OF DATA ON CASES REPORTED IN THE LITERATURE OF SCLERODERMA WITH ESOPHAGEAL LESIONS

Total cases reported		32
Sex: male 7, female 25.		
Dermatologic classification		27
Acrosclerosis	21	
Scleroderma (generalized)	4	
Acute edematous scleroderma	1	
Localized scleroderma	1	
Roentgenologic features		24
Stenosis in lower part of esophagus	8	
Retardation, lack of motility	11	
Dilatation or cardiospasm	5	
Esophagoscopic features		8
Stenosis in lower part of esophagus	5	
Changes restricted to esophageal walls	3	
Cases with necropsy		8

whose monumental chapter with Brünauer in the Jadassohn Handbuch is a storehouse of information on this disease. He made an esophagoscopic study of the patient and observed changes in the esophageal wall. In 1916 Schmidt[65] reported the roentgenologic appearances in a patient suffering from scleroderma and dysphagia, and although he found no lesion, there was delay in passage of the barium into the stomach. In 1923 Schwarz[66] described esophagitis in scleroderma. In 1930 Nomland[52] observed dilatation of the esophagus by means of roentgen study. Rake[63] in 1931 described gross and microscopic postmortem findings in a case of scleroderma in which there had been contraction in the lower end of the esophagus roentgenologically; 6 years earlier the organ showed dilatation, with no muscular hypertrophy. In its upper third erosions were present in an intact mucosa, but in the middle and lower thirds the mucosa was lacking (postmortem digestion?). The submucosa was thickened and infiltrated with cells, chiefly mononuclear and polymorphonuclear in type. In 1932 Fessler and Pohl[17] reported regional stenosis in the lower end of the esophagus. They had also reviewed the literature to that time and found that the esophageal lesions had been called cardiospasm (Nomland), esophagitis (Schwarz), diverticulum (Ehrmann) and atony (Schmidt).

Other reports of from 1 to 36 cases (Olsen *et al.*) have appeared: Tsukada;[73] Kuré; Yamagata; Tsukada and Hiyoshi;[40] Hiyoshi;[30] Weissenbach *et al.*,[78] Hoesli[31] (a thesis on functional disturbances and lesions of the esophagus in scleroderma); Weissenbach, Martineau, Bouwens, Pizon and Matteo;[79] Barasciutti;[3] Ochsner and DeBakey;[54] Dowling;[13] Goetz and Cole Rous;[22] Thomas;[72] Jackman;[33] Lindsay, Templeton and Rothman[45] (5 cases of lesions of the esophagus in generalized progressive scleroderma with detailed literature); Weiss, Stead, Warren and Bailey;[76] Hale and Schatzki;[27] Kanee;[35] Pugh, Kvale and Margulies;[61] Bevans;[6] Olsen, O'Leary and Kirklin;[58] Goetz;[21] Rafsky and Herzig;[62] Schatzki;[64] and Dostrovsky.[15] The papers of Lindsay, Templeton and Rothman, Olsen, O'Leary and Kirklin, and of Goetz deserve full study by the reader.

There is general agreement in the literature that the esophageal processes associated with scleroderma are the result of the presence of sclerodermatous changes in the walls of the esophagus. While there may be differences resulting from individual variation in the patients studied, there is on the whole agreement upon the findings. Most of the patients suffering from scleroderma or acrosclerosis with esophageal disturbances are women. This may be merely a reflection of the greater incidence of scleroderma in women. Weissenbach *et al.*,[77,80] 16 of 18 cases were women; Hale and Schatzki, 15 of 22 patients were women; Olsen, O'Leary and Kirklin (literature) 25 female and 7 male; (personal cases) 36 cases—24 female, 12 male). The patients complain of progressive dysphagia in some cases early in the disease. Weissenbach *et al.*, however, believe that the dysphagia is an early symptom only if the face and oral cavity are involved early. Hale and Schatzki found that 15 of 22 patients had no definite swallowing symptoms, while dysphagia was present in 7. Lindsay, Templeton and Rothman noted considerable variation in the severity and the time of onset of esophageal symptoms and considered this as characteristic. Only one of their 5 patients volunteered any complaints referable to swallowing. In the remaining 4 cases the symptoms were brought out on questioning but

the pain and discomfort from the cutaneous lesions caused the difficulty in swallowing to be overlooked. These authors worked out changes in muscular movements observed by fluoroscope and their findings will be discussed later. Olsen, O'Leary and Kirklin found the esophageal disturbance responsible for the symptoms of which the patient complained primarily. Actually they believed the esophageal disturbance was most often a delayed manifestation of the disease (Cf. Hoesli). Goetz showed the range of symptoms referable to involvement of the esophagus as exemplified by the findings in one of his patients. "The esophageal disturbances in our patient consisted in difficulty in swallowing, the sensation of blockage behind the sternum associated with cramp-like burning pain; nausea and regurgitation followed by relief on vomiting."

The radiologic findings in the esophagus have long been reported on. Among those who have paid special attention to this aspect of the problem are Schmidt, Kuré *et al.*, Weissenbach *et al.*, Weiss *et al.*, Ochsner and DeBakey, Jackman, Goetz (Goetz and Cole Rous[22]), Lindsay, Templeton and Rothman; Olsen, O'Leary and Kirklin; Hale and Schatzki; and Schatzki.

In 1916 Schmidt[65] studied a patient suffering from scleroderma and dysphagia and noted delay in the passage of barium sulfate (15 minutes was required for passage of the barium into the stomach). Kuré and his associates[40] made roentgen-ray studies in 5 patients with scleroderma. Only 2 of them complained of dysphagia but in all there was great retardation in the passage of a test meal especially when the patient was in the dorsal decubitis position. The greatest delay was in the cardia. Weissenbach and his associates, using Kuré's technic, found in addition to the retardation of the bolus, that the normal peristaltic movements were absent and that there were a gaping of the esophagus and a tendency for the barium meal to adhere to the walls of the esophagus. Weissenbach, Stewart and Hoesli[80] summarized the roentgenographic findings in their cases as follows: 1) normal morphologic appearance of the esophagus; 2) retarded and complete descent of the opaque bolus with partial adherence to the esophageal wall; 3) accentuation of findings in the recumbent position and 4) evidence of esophageal blockage in some cases without clinical and subjective symptoms. Lindsay, Templeton and Rothman on the basis of their 5 cases stated that the esophageal disturbances are characterized by "loss of peristalsis in the lower two thirds, with relaxation and mild dilatation of the lower two thirds down to the phrenic ampulla, and probably some atony of the cardiac sphincter. This occurs as a direct result of the sclerodermatic process. Difficulty in swallowing solids or liquids especially when in the lying position, due to delayed emptying of the esophagus, burning pain behind the sternum about an hour after meals, worse on lying down and particularly on lying on the left side, due probably to regurgitation of gastric contents into the esophagus, and resulting chronic esophagitis, chronic ulceration of the lower third of the esophagus, localized chiefly to the region just above the phrenic ampulla. This is probably a direct result of the esophagitis with sclerodermatic changes as a predisposing factor. Stricture formation in the later changes is limited to the region immediately above the phrenic ampulla of the esophagus."

Dilatation of the esophagus with retardation of barium at the cardia was noted by Rake,[63] by Nomland[52] and by Jackman,[33] as well as by Rafsky and Herzig[62] who spoke of cardiospasm.

Stenosis of the cardiac end of the esophagus has been noted fairly often (Dowling; Fessler and Pohl; Lindsay, Templeton and Rothman; Olsen, O'Leary and Kirklin; Weiss *et al.*). Goetz noted dilatation of the middle third of the esophagus, narrowing of the lower third; delay in emptying and residual food and mucus as well as ulceration.

The roentgenologic appearance of the esophagus in scleroderma has been the interest of Hale and Schatzki. These radiologists, during the 5 years an abnormal esophagus. Eight patients who were without symptoms showed abnormalities. There was no correlation of the extent of the cutaneous and esophageal changes. While the roentgenologic appearances of the abnormal cases were not uniform, they showed a distinct pattern consisting mainly in delayed emptying, combined with a decrease in the peristalsis of the esophagus) (Cf. Lindsay *et al.*). Olsen, O'Leary and Kirklin noted conclusive roentgenographic features in 15 cases.

TABLE 2. DATA CONCERNING THIRTY-SIX CASES OF ACROSCLEROSIS OR SCLERODERMA IN WHICH THERE WERE ESOPHAGEAL SIGNS OR SYMPTOMS

I. 18 cases with positive roentgenographic or endoscopic observations
  A. Age distribution: 34 to 61 years
  B. Sex: female 13, male 5
  C. Dermatologic diagnosis: acrosclerosis, 18
  D. Roentgenologic diagnosis, 18 cases
    1. Esophageal dilatation or cardiospasm, 6
    2. Hiatal hernia, 9
    3. Negative results of examination, 3
  E. Esophagoscopic diagnosis, 8 cases
    1. Hiatal hernia (corroborated roentgen diagnosis), 5
    2. Sclerodermic involvement in patient with esophageal dilatation (by roentgen study), 1
    3. Sclerodermic involvement of esophageal wall not shown by roentgenologic examination, 2
  F. Passage of sounds, 7 cases
    1. Diagnosis and treatment of cardiospasm, 3
    2. Dilatation of stricture associated with hiatal hernia, 4
II. 6 cases with negative roentgenographic findings and no endoscopic studies
  A. Age distribution: 23 to 60 years (average 44)
  B. Sex: female 2, male 4
  C. Dermatologic diagnosis: acrosclerosis 4, scleroderma 2
III. 12 cases with neither roentgenographic nor endoscopic studies
  A. Age distribution: 17 to 66 years (average 35)
  B. Sex: female 9, male 3
  C. Dermatologic diagnosis: acrosclerosis 11, scleroderma (acute), 1

* In 2 of these cases esophagoscopic examination demonstrated changes in the esophageal wall. In the remaining case a diagnosis of cardiospasm was made by passage of sounds.

prior to publication, studied the upper gastrointestinal tract of 22 patients with scleroderma of variable duration. As noted above, only 7 of the patients had definite dysphagia although in 6 of the asymptomatic group careful questioning disclosed that a sensation of material remaining in the mid chest and occasionally localized burning or pain following the hurried ingestion of food, or after eating a large meal had been noticed. Five of 7 with dysphagia had Their findings are summarized in the table.

Esophagoscopy is rarely practiced on patients with scleroderma, according to Weissenbach, Stewart and Hoesli,[80] because of narrowing of the oral orifice and atrophy of the buccal mucosa. Nonetheless there are observations on a few patients obtained by this means. Ehrmann[15] noted thickening of the esophageal wall; Schwarz described esophagitis; Lindsay, Templeton and

Rothman in repeated study of 4 of their 5 patients found inflammatory changes in the lower two thirds of the esophagus, with a diffuse white membrane in the lower part of the esophagus, about 4 or 5 cm. above the diaphragmatic level. Goetz recorded spasm on withdrawal of a dilator which passed easily into the stomach. Olsen, O'Leary and Kirklin performed esophagoscopic examination in 8 cases, and passed esophageal sounds in 7 of the 18 cases in which roentgenographic or endoscopic evidence was conslusive, over previously swallowed threads.

Histologically the changes in the esophagus have been studied, by Rake; Weissenbach *et al.;* Kuré *et al.;* Freudenthal;[19] Lindsay, Templeton and Rothman; Goetz, and by Bevans, and Ochsner and DeBakey. All found erosion of the mucosa, thickening of the submucosa, hypertrophy of the muscularis mucosae and atrophy of the muscular coats. Thomas reported an acute ulcer in his case. Goetz was the first to describe leukoplakia and calcification. Other findings in Goetz's case were marked hypertrophy of the muscularis mucosae, the presence of lymphorrhages, the marked disintegrative changes in the muscular layers (myositis), the extensive involvement of the myenteric plexus. Freudenthal had described lymphorrhages as a feature common to the muscular lesions of both scleroderma and dermatomyositis. Clinically, 8 of Goetz's 13 cases were affected with similar changes. All 3 cases coming to autopsy showed chronic ulcus.

Bevans[6] found replacement of the mucosa of the esophagus by fibrinoid material, the submucosa sclerotic, muscle layers atrophic and extremely fibrosed (Cf. Rake).

Differentiation of the esophageal complaints must be made from cardiospasm, hiatal hernia, shortening of the esophagus as it occurs in persons who are obviously normal. Complete discussion of the differential considerations of these processes from the organic changes in the esophagus in scleroderma is contained in the study of Olsen, O'Leary and Kirklin.

Lower Gastrointestinal Tract. Relatively little mention has been made in the literature about involvement of the gastrointestinal tract in scleroderma. Goetz stated that when he and Cole Rous in 1942 reported their case of scleroderma with duodenal stasis, the first in which the features of small bowel lesions were demonstrated radiologically, they could find only 2 similar lesions in the literature (Kraus,[39] Rake[63]). Since then other reports have appeared. Hale and Schatzki and later Schatzki described the roentgenological appearance of the gastrointestinal tract in scleroderma. A summary of their findings follows:

The Stomach. The stomach was examined in 22 patients. In some cases there was considerable delay in emptying; in some there was spasm of the antrum. The authors thought the significance of these changes, however, is doubtful.

The Small Intestine. Four of the 18 patients in whom the small intestine was studied showed remarkable changes roentgenologically. In 1 of the 4 cases the intestinal symptoms and the appearance of the intestine stood in the foreground, and the presence of scleroderma was discovered later more or less accidentally, whereas in the 3 other cases scleroderma had been present for many years. The small intestine showed significant changes in 4 patients. There was localized widening, usually of the proximal loops, together with marked delay in the passage of barium through these dilated loops. Recognition of these changes

in the small intestine appears to be of particular clinical importance.

The Large Intestine. Two of the patients with scleroderma showed an unusual appearance in the large intestine which is difficult to explain on the basis of any other pathology, and the authors therefore assume that it is related to their scleroderma.

Pugh and his co-workers in 1945[61] also reported on a patient with gastrointestinal involvement. They found that peristalsis in the small intestine was definitely sluggish and segments were seen to remain without normal contractibility for a considerable period before ineffective peristalsis would begin again. The relative lack of contractibility was seen especially in the terminal portion of the ileum.

Bevans[6] has made a study of the pathology of scleroderma with special reference to the changes in the gastrointestinal tract. In both of her cases, the remainder of the gastrointestinal tract showed extensive, although patchy, changes. There was but little thickening of the submucosa in either case. There was diffuse dilatation of the colon demonstrated by barium enema in her Case 1 because of muscle atrophy. (Matsui mentioned hypertrophy of the muscularis mucosae but atrophy of the muscularis propria.) In Bevans' cases either no change in the muscularis mucosae or atrophy was observed. Edema was present in the muscularis adjacent to areas of muscle atrophy. This latter change is in accord with the general pattern of the disease as it is seen in the skin in the form of edema, indurations and atrophy. There were outstanding vascular alterations in the gastrointestinal tract. Bevans cites a third patient with diffuse scleroderma, under observation for 3 years in the Goldwater Memorial Hospital, who developed signs of intestinal obstruction. Adhesions between intestinal loops were found at operation. No point of obstruction was determined but the small intestine was diffusely dilated. Death followed 12 hours later but no autopsy was performed.

Goetz believes that the gastrointestinal lesions in cases of scleroderma are not as rare as the literature would make us believe and it appears from his cases that duodenal stasis is, like esophaegeal spasm, one of the earlier visceral manifestations of diffuse scleroderma. Five of his cases had identical pronounced changes in the intestinal tract. The most prominent radiological appearances were paralysis and lack of peristalsis particularly affecting the duodenum and the jejunum with localized widening of individual loops and breaking up of the barium. In one case this was so marked that there was a duodenal residue after 24 hours and in another case the dilatation involved the whole small bowel so that the diagnosis of paralytic ileus was made at the time and laparotomy contemplated.

In the large bowel the most characteristic lesion on radiological examination according to Goetz, was narrowing and rigidity and the appearance of sacculation. However, this narrowing may not be confined only to the large bowel and in one case Goetz saw it in the terminal ileum, simulating regional ileitis. When first observed, these features were very puzzling and disputable, but when at autopsy narrowing and dilatation could be confirmed in all cases it became evident that these changes had to be regarded as integral and important clinical features of scleroderma.

In one patient studied in detail there were the following pathologic changes: 1, marked atrophy of the bowel wall; 2, fibrous replacement of muscle fibres with occasional lymphocytic and plas-

ma cell infiltration; 3, prominence of the neuromuscular apparatus.

The prominence of the neuromuscular apparatus was accompanied by a conspicuous absence of ganglion cells and fibrosis in some cases. This suggested to Goetz that the motor activity of the bowel was interfered with by some intrinsic nervous disorder brought about by the affection of the intramural neuromuscular apparatus, similar to what he had seen to be the case in the esophagus. In this connection Goetz calls attention to the investigations of Rake (1926, 1927) and Etzel (1942) in cases of achalasia of the esophagus. These authors regularly found fibrosis of the myenteric plexus with poverty of ganglion cells. Etzel (1942) suggested vitamin B deficiency as the responsible etiological agent. However, none of Goetz's patients showed signs of any of the known vitamin deficiencies. Indeed, if any signs of avitaminosis had developed one would not have been surprised in a case which suffered from difficulty in swallowing for 14 years. However, the radiological appearances of the bowel are very similar to those of a vitamin deficiency. For this reason all of Goetz's patients were treated intensively with all known vitamins with no effect except in one case in which duodenal stasis was present before, but absent after treatment. In this patient leukoplakia of the esophagus was found, present ever since the time she first complained of dysphagia, achlorhydria was present. However, the blood was always normal.

In passing, it is worthy of note that little has appeared in the literature recently on hepatic involvement by scleroderma. For example, Harvier and Bonduelle[28] observed a case of progressive scleroderma with hepatolienal calcification and in 1934 Milbradt[49] presented a patient with atypical diffuse scleroderma with Osler's syndrome (telangiectasia) and hepatic disturbance.

Cardiovascular Involvement. A variety of circulatory lesions have been observed in generalized scleroderma, (Hektoen;[29] Masugi and Yä-Shu[47]). An outstanding feature of this disease is vasoconstriction. Specific, that is sclerotic, changes in the heart muscle due to proliferation of connective tissue between the muscle fibers, myocarditis, dilatation of the aorta, and pericarditis, are among the changes which have been reported in the older literature. Newer studies have re-emphasized the circulatory features of this disease and have lent additional support to the idea that scleroderma is more than a cutaneous process. However, the mere presence of a cardiac or vascular lesion in a patient with scleroderma does not of necessity establish the sclerodermatous nature of the circulatory system disease. On the other hand, Johnson[34] has added somewhat to the complexity of this relationship by emphasizing the disabling changes in the hands resembling scleroderma following myocardial infarction.

In contrast to disturbances of the gastrointestinal tract, clinical evidence of cardiac involvement may occur late in the course of the disease, but Weiss and co-workers[76] in their careful study of sclerodermal heart disease, noted that in 3 cases the appearance of cardiac symptoms preceded changes in the skin by as much as 2 years.

They conclude that the evidence from 9 patients points toward the interpretation that the myocardial lesions are an integral part of scleroderma. "The sequence involved in the development of the myocardial lesions were those of overgrowth of connective tissue, as in the skin, but the character of the connective tissue in the skin and myocardium in scleroderma was dif-

ferent. However, the changes in the 2 patients with scleroderma studied at post mortem examination were similar and differed in several significant respects from other varieties of myocardial scars. The pathologic observations together with the clinical data in the cases of the series indicated that scleroderma heart disease is a clinical and pathologic entity."

All of Goetz's patients suffered from dyspnea, orthopnea and cyanosis and one of them presented the picture of a black cardiac. The heart in most of his cases was small, the blood pressure and the cardiac silhouette normal. However, the diagnosis of scleroderma heart was made from the kymogram which showed marked blunting of the cardiac excursions.

Goetz noted that the histology of the heart in patients coming to autopsy at first sight appeared very heterogeneous, revealing 3 different types of lesions: 1, scattered foci of fibrosis in apparently normal muscle fibres; 2, frank fibrosis of the entire thickness of the myocardium extending from the pericardium to the endocardium; 3, a diffuse lesion showing marked disintegration of the muscle fibres which were interlaced with coarse bundles of connective tissue which was highly vascular.

This third lesion is obviously the forerunner of the second type. All intermediate stages were observed. From these observations it became evident that myocardial fibrosis was not the result of vascular interference. This was supported by the lack of sufficient pathological changes in the coronary arteries, the pattern of the fibrosis and the absence of hemosiderin pigment in the connective tissue. The earlier lesions of this fibrous replacement were observed in another case. They reminded Goetz of what has been described in early cases of dermatomyositis as "angiomyositis." Detailed findings indicate that the heart lesion is an integral part of scleroderma.

Despite the marked fibrosis the electrocardiogram did not show great change in one of Goetz's cases. In others, however, the electrocardiogram was grossly abnormal, the tracings ranging from bundle branch block to auricular fibrillation. In one of his patients all the heart beats were extrasystoles which originated from 8 different foci.

The intense cyanosis and orthopnea in these cases has had little attention. One case was classed as Ayerza's disease (black cardiac). Goetz believes that pulmonary vascular lesions plus thickening of the alveolar septa, compensatory emphysema and some degree of rigidity of the thorax due to involvement of the muscles, and the hemodynamic disturbances resulting from myocardial fibrosis adequately explain the cyanosis as being due to anoxia. In one case this explanation was supported by an increasing erythrocytosis and increasing hemoglobin in the blood as the disease progressed.

In one of Bevans' patients pericarditis was present and appeared to be both recent and old. According to Lewin and Heller,[43] pericarditis was present in 8 of 29 cases of scleroderma observed at necropsy. In some of these cases with other conditions associated (especially tuberculosis and rheumatism), the accompanying pericarditis cannot be definitely attributed to scleroderma. In Bevans' cases the lesion in the pericardium presented a hyalinization of collagenous tissue which was reconcilable with the lesions of scleroderma in other parts of the body. In her Case 1, the acute lesion overlying the chronic fibrous pericarditis was diffuse and too advanced to be included among those related changes which sometimes occur in

uremia. Since there were similar thickening and hyalinization of other serous membranes, particularly the peritoneum, it seemed justifiable to Bevans to include those in the pericardium as part of the disease, scleroderma, and not as manifestations of the uremic state.

Endocrine Gland Involvement. The volume of literature on this phase of the scleroderma question is so large and so controversial that a separate study and analysis of even a few years' production would be necessary for an adequate appraisal. Accordingly, in this general summary of the visceral manifestations of scleroderma only trends can be indicated. It is pertinent to call attention at this point to a few of the previous collections of data on the endocrines and scleroderma. It is necessary, however, to indicate that the views expressed are usually conjectural, contradictory and generally inconclusive as to the precise connection of the endocrine symptoms to scleroderma. The situation remains the same today. Castle[9] in 1923 and Boardman[7] in 1929 made extensive reviews of the literature which are worthy of study in the original. Other reviews are available by Seale,[67] and by Ehrmann and Brünauer[16] in Jadassohn's Handbuch. The best-established relationship between the endocrines and scleroderma is a disturbance in calcium metabolism. This will be discussed below. Thyroid symptoms in scleroderma have received much attention. Abnormal (high or low) basal metabolic rates have been observed (O'Leary and Nomland[56]) and thyroid medication has on occasion been beneficial. On the other hand, Haldin-Davis[26] was unable to find evidence of scleroderma in 100 patients with thyroid disease. Ovarian dysfunction too has been reported in scleroderma. The literature in this phase has been ably summarized by Wiener[81] as follows: "Amenorrhea, dysmenorrhea, onset of the disease in pregnancy and in the spontaneous and induced menopause, findings of ovarian changes, the therapeutic success of estrogens, and the 3 to 1 predominance of the female sex are reasons enough to consider the *gonads*. The situation is similar with regard to the pancreas, thyroid and pituitary." Not always, however, is widespread endocrine gland involvement so clear-cut. One recent example will suffice. In her careful study of 2 patients, Bevans[6] found no definite lesions in the parathyroid glands (1 case), the pituitary glands, and the adrenal glands (2 cases). The thyroid gland in one case showed moderately increased fibrosis and proliferative lesions in the vessels; Case 2 showed more extensive involvement of the entire gland. Neither patient had shown clinical signs of thyroid dysfunction.

Calcium Metabolism. Disturbance of calcium metabolism is consistently found in scleroderma. This is especially prominent when scleroderma occurs together with calcinosis such as is the case in so-called Thibierge-Weissenbach syndrome. Since there is evidence that scleroderma may in some way be related to hyperfunction of the parathyroid gland and since the latter has a definite relationship to calcium metabolism, it is apparent that this may be the basis for the disturbed calcium metabolism. There is an extensive background in the literature for this concept. It has been reviewed in extenso by Cornbleet and Struck,[10] Goetz[22] and Basch.[4]

This calcinosis in the subcutaneous tissue in cases of scleroderma has been known since 1878 (Weber[74]). In 1910 Thibierge and Weissenbach[71] described a personal case and reviewed 8 others from the literature. Subsequently numerous authors described cases and in

1932 Basch[4] (a follower of Weissenbach's) in a comprehensive thesis collected as many as 46 cases from the literature. Since then, this syndrome has become known as the Thibierge-Weissenbach syndrome. It occurs almost exclusively in women, often suffering from ovarian hypofunction, and is preceded by or associated with vasomotor disturbances, parasthesias, acrocyanosis and angiospasm, and Raynaud's syndrome, especially of the upper extremities, resulting in sclerodactylia.

The calcinosis is regularly deposited and affects parts of the body subjected to pressure; that is, the tips and the volar surfaces of the fingers, the arms along the ulnar border, the elbows, the skin along the shin and in front of the patella and over the tuber ischii. This distribution suggests that trauma may be the *precipitating* cause.

Two types of calcinosis have been distinguished: (a) calcinosis circumscripta and (b) calcinosis universalis. In the former the calcium deposits are located in the subcutaneous tissue only but in the latter they also occur in the mesenchymal tissue as well. Calcinosis circumscripta occurs in the Thibierge-Weissenbach syndrome.

Goetz has ably analyzed the recent literature on this problem as follows: "Numerous theories have been advanced to explain the pathogenesis of calcinosis but 'in spite of the ever-increasing volume of literature on the subject one is confused by the increasing complexity of the theoretical considerations' (Brody and Bellin, 1937). It is natural that the calcium metabolism should have been incriminated and the literature on that subject has grown to a considerable volume. Those who are interested should consult the excellent article by Brooks (1934). Most authors found normal serum calcium and blood phosphorus levels and this could be confirmed in our patient. However, as Bauer, Marble and Bennett (1931) put it, the serum calcium shows only the height of the stream and not its direction. Calcium balance studies are therefore essential in these cases. Only a few reports are available. Bauer *et al.* (1931), Paggi (1934), and Cornbleet and Struck (1937) reported a tendency to retain calcium and phosphorus following probably normal absorption. In all our cases the calcium balance was negative which is in agreement with reports by Dowling (1940) and Byron and Michalover (1943). In addition the serum phosphatase was normal and there was no decalcification of the bone.

"In this connection, it is the parathyroids which have been blamed more than any other agent on account of their known role in calcium metabolism and both scleroderma and calcinosis have been considered to be due to disturbances of these glands (Selye, 1932; Weissenbach *et al.*, 1933; Leriche, 1935; Leriche and Jung, 1935; and Kusunoki, 1939). Selye reported that following intraperitoneal injection of as little as 5 units of parathyroid extract, sclerodermatous lesions with calcific deposits in the skin developed in 20% of his rats. Following this concept, Leriche (1935) suggested parathyroidectomy and his good results were supported by some; other authors could not substantiate them (Dowling, 1940 and Byron and Michalover, 1943). Obviously hyper-parathyroidism could not account for all the clinico-pathological features of our case of scleroderma."

Nervous System Manifestations of Scleroderma. Although in the past a number of nervous system manifestations (central and peripheral) of scleroderma have been reported, these are certainly uncommon. Furthermore, their exact relationship to scleroderma is much less well established than the

associated lesions in some other organs. The same considerations apply to the later literature.

In Kanee's[35] case, Duryee, in personal communication, reported that electroencephalographic studies revealed a moderate degree of diffuse electrocortical activity. Duryee has found this in over 80% of cases of generalized scleroderma. Bevans stated that: "changes in the central nervous system were studied extensively by Dr. Abner Wolf and were not considered noteworthy in the present connection. Unfortunately the sympathetic ganglia were not studied. The sympathetic plexuses in the gastrointestinal tract showed no structural alteration. Whether lesions of the sympathetic system are responsible for the spasm exhibited roentgenologically in the gastrointestinal tract awaits investigation. To date, the results of sympathectomy for Raynaud's syndrome in patients who develop scleroderma have been variable and not encouraging."

Guss[25] reported in 1947 what he considered to be the second patient with scleroderma in whom convulsions occurred. From the facts and the author's own analysis, this patient's disorders really had a vascular rather than neurogenic origin. At any rate the precise sclerodermatous nature of the nervous system manifestations in this case is not evident.

Skeletal Muscle Involvement. Involvement of skeletal muscle in cases of scleroderma has been known for about 80 years. Since the first description of this lesion much work has been done to show that scleroderma and dermatomyositis are variations of one process (Nixon, 1907[51]; Langmead, 1923[42]; Dowling and Griffiths, 1939[14]; Lewis, 1940[44]; Dowling, 1940[13]; Freudenthal, 1940[19]; and Griffiths, 1940[24]) or are actually 2 different diseases (Weber and Gray, 1924[75]; Brock, 1934[8]; Kinney and Maher, 1940[37]; Keil, 1940[36]; O'Leary and Waisman, 1940[57]; and Horn, 1940[32]) Brock, 1934,[8] in his review of the literature, noted that it is difficult to distinguish between scleroderma and dermatomyositis from histopathologic or clinical features during the early stages. But as induration and sclerosis advance, differences in the clinical picture as well as the histopathology become characteristic (Cf. O'Leary and Waisman). In scleroderma the inflammatory infiltrations at the later stage are minimal and perivascular cell infiltration is present in small foci only. The vessels become thick, their lumen narrow and often occluded followed by recanalization. There is proliferation of connective tissue fibres with subsequent sclerosis, hyalinization and calcareous degeneration. The muscle fibres undergo secondary degeneration which is in direct proportion to the degree of sclerosis.

In dermatomyositis, Brock[8] finds that the diffuse infiltration of lymphocytes and plasma cells in the cutaneous, subcutaneous and the muscular tissue remain the outstanding feature to the end. Perivascular infiltration is another prominent feature. The degeneration of the muscle fibres is marked and dependent on the inflammatory process. The changes in the vascular and connective tissue are minimal.

The difficulty of really distinguishing between the 2 processes is emphasized by Goetz's patient in which the findings suggest that he was dealing with a type of case which forms a connecting link between scleroderma and dermatomyositis.

Bones and Joints. The involvement of bones and joints by the sclerodermatous process is so well known and accepted that little new has been added to our knowledge recently. Jackman[33] in his study of the roentgen features of scleroderma and acrosclerosis in 4

cases noted that although the most striking feature is calcinosis usually involving pressure points on the skin, another finding is the slow progressive absorption of the distal phalanges of the fingers. This occurs more often in acrosclerosis and does not become marked until the disease has been present for years. Terminal absorption may be associated with calcinosis and occasionally with increased intraosseous deposition of calcium. Synostosis between the distal and middle phalanges may occur.

Eye. Although cataracts have been reported occurring with scleroderma, it might be stated in passing that Werner's syndrome (progeria in the adult), a heredofamilial disorder with scleroderma, bilateral juvenile cataract, precocious graying of the hair and endocrine stigmatization so well described by Oppenheimer and Kugel in 1934 and 1941[59] should not be properly included in this discussion on scleroderma in spite of the many manifestations of this process also associated with scleroderma. Thannhauser[70] in an extended study in 1945, showed that the title scleroderma with cataracts is misleading and that the cutaneous changes in this anomaly are not those of true scleroderma. The same can be said of Rothmund's syndrome, a process in which cataracts are associated with a peculiar degeneration of the skin. Thannhauser proposes that the cutaneous lesions of Werner's syndrome be called "heredofamilial atrophic dermatosis with skin ulcers," and that of Rothmund's syndrome "heredofamilial atrophic dermatosis with telangiectases."

Miscellaneous Involvement. Abnormalities in other structures have been found in a small number of cases. It is open to serious question whether these effects are sclerodermatous or merely coincidental findings. Among the organs involved are the kidneys, the teeth and gums, the uterus, and the prostate. Bevans, for example, found extensive renal lesions in both of her cases. The medium sized and smaller arteries were especially involved. The glomerular lesions were similar to those found in lupus erythematosus. Tubular alterations were severe, and the renal pillars were thickened. The larger vessels in the peripelvic fat showed the same type of perivascular fibrosis as that observed in other parts of the body. The pathologic findings were far in excess of the clinical and laboratory data indicating renal disease. Although uterine atrophy had been noted by others, no such change was observed by Bevans in her first case. However, the lamina propria of the vagina and external cervical os shared in the generalized connective tissue thickening that occurred in the skin and elsewhere. The ovaries appeared to be normal. The smooth muscle in the prostate of Case 2 appeared to be atrophic and could, according to Bevans, represent sclerodermatous rather than involutional change.

Retraction of the gingival margins with loosening of the teeth have been noted in the older literature of scleroderma. Davis and Saunders (1946)[11] have recently presented a case of scleroderma involving the face and gingiva. In a careful study Stafne and Austin[69] observed radiographically a characteristic dental abnormality in acrosclerosis and scleroderma. It is an increase in the width of the peridontal space, which, when it does occur, is sufficiently characteristic to cause the presence of acrosclerosis to come to mind. Among 127 cases of acrosclerosis and scleroderma at the Mayo Clinic, 9 (7.08%) had this anomaly. It occurred in 4 men and 5 women of 36.9 years average age. Eight of the patients had acrosclerosis and 1 had

scleroderma. While all the teeth may be affected, the posterior are involved more than the anterior. Microscopical examination of 1 specimen showed that the increased periodontal space is occupied by markedly thickened periodontal membrane. The thickening of the vessel walls suggests to the authors that the change in this membrane is probably produced by the circulatory disturbance which is a salient feature in acrosclerosis and diffuse scleroderma. Sometimes certain cases of scleroderma are complicated by other diseases which, while unrelated, may improve under therapy for the scleroderma. Kusunoki and Kuwabara[11] reported a case of diffuse scleroderma accompanied by leukemia which improved following parathyroidectomy. While this suggests the probable value of blood studies in scleroderma, the therapy can by no means be considered applicable to the general therapy of leukemia.

Because it summarizes the present-day status of scleroderma so well and so succinctly, we quote the conclusion of Goetz's comprehensive survey of the visceral manifestations of scleroderma: "Obviously the term 'scleroderma' should be abandoned. It is quite evident today that we are dealing with a systemic disease neither solely nor primarily involving the skin. 'Scleroderma' is only the obvious and striking symptom of a generalized disease and the most serious symptoms actually arise in the viscera.

"Now that the visceral changes are being more widely recognized as an integral part of the disease, the systemic implications will receive much more consideration than the dermatological aspect. Physicians will be more on the look-out for these changes and undoubtedly more reports will appear in the literature. It appears therefore to the writer that now is not an inopportune time to abandon the term 'scleroderma' which for so long has obstructed investigation into the cause of that disease and to replace it by one more descriptive of the true state of affairs. The term 'sclerosis' already being in use, it appears that '*Progressive systemic sclerosis*' would describe the condition adequately until such time as the etiology has been established. Scleroderma is then only one of the symptoms or signs of progressive systemic sclerosis.

"Progressive systemic sclerosis may be defined as an induration and sclerosis which may occur in any organ inclusive of the skin, the muscles and the blood vessels. Pigmentation, loss of weight, asthenia, arthritis and other symptoms occur, depending on the degree and extent of the sclerosis. Everywhere the same changes occur, *viz.*, edema, followed by proliferation of connective tissue and sclerosis of collagenous bundles, resulting in many cases in atrophy of the organ concerned. This may occur in the connective tissue of the skin, in the interstitial tissue between the alveoli of the lungs, the acini of the liver, in the kidney, the muscle fibres of the heart, within the pulp of the spleen and in the endocrine glands."

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A PSYCHOSOMATIC APPROACH TO VASOMOTOR RHINITIS

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For many years vasomotor rhinitis has been recognized as a disorder in which emotional factors may play an etiological role. Some textbooks of otolaryngology include "psychic disturbances" in a list of possible causes and mention two old synonyms, "intermittent neurotic catarrh" and "nervous coryza." Almost nothing is said, however, about what the emotional problems are or how they exert their effect.

On the basis of clinical and experimental studies it appears that psychogenic factors may play a part in at least 3 ways: 1) the result of fear or anxiety, 2) the result of a conflict and 3) the result of direct suggestion. These mechanisms will be discussed in some detail and then considered in their interrelationships to other etiological factors.

For the purpose of this discussion, Lederer's[4] definition of vasomotor rhinitis will be used. He defines the entity as "a condition characterized by intermittent engorgement of the nasal mucosa, sneezing associated with a free flow of diluted mucus and nasal obstruction." There have been efforts to sub-type cases on etiological and pathological grounds and it seems likely that a number of dissimilar processes are grouped under a single heading.

The first pattern in which emotional factors play a causative part occurs as a reaction to impending danger. In response to fear there is an initial vasoconstriction which is followed by a vasodilatation. This is comparable to the local effect of epinephrine. The clinical picture in the "after-phase" is that of vasomotor rhinitis.

Vasoconstriction within the nose in response to fear is part of a general homeostatic adaptation which prepares the organism for fight or flight. According to Post,[7] when the body is alerted for action, changes occur which prepare the nose to accommodate an increased oxygen intake. The airway is enlarged and a greater mucus production is provided to moisten the added air volume. To accomplish the former the size of the turbinates is altered by the smooth muscle tissue distributed about arterial and venous tracts and in the walls of the spaces of erectile tissue. These structures are innervated by sympathetic fibers.

Post's[7] observations have added to our knowledge of the effect of fear on the nose. Studying a group of returning combat men who continued to react as though they were in dangerous situations, he noted a vasoconstriction within the nose. The after-phase response was that of blockage due to a relaxation and turgescence of the erectile tissue within the turbinates. In other words, the veterans continued

to react as though they were facing a threatening situation even though they were safely back in the United States.

It is important to realize, further, that the clinical picture of vasomotor rhinitis may be produced by any unconscious, internal conflict which gives rise to anxiety, just as it is produced by an external danger or recent and repeated exposure to situations which give rise to fear. A "forbidden" wish which threatens to erupt into consciousness and to create conflict will stir up anxiety which results in a reaction that parallels the response to a terrifying experience. In both instances the effect follows sympathetic nervous system stimulation and is only one in a series of tension responses.

A second pattern in which emotional factors are important has been described by Wolff *et al.*[11] In their group of experimental subjects, changes were observed in the nose after unsympathetic discussion of pertinent and conflictual problems. These changes consisted of an "initial hyperemia associated with turgescence of the erectile tissue in the turbinates, . . . engorgement of the nasal mucosa and increased secretion. Often after the subsidence of hyperemia, secondary pallor ensued with the mucous membranes of the nose remaining boggy and edematous." The authors believed that the impulses which effected the changes were carried by the vagus nerve. The primary picture was principally that of vasodilatation while the secondary one was that of edema.

A case reported by Fowler[3] points to the conclusion that an autonomic imbalance with a preponderance of parasympathetic (or a decrease in sympathetic) activity results in the clinical picture of vasomotor rhinitis. In his patient a unilateral disturbance developed on the side on which the stellate (sympathetic) ganglion was removed.

According to Proetz[8] the autonomic nervous system "functions below the level of consciousness, is not subject to the control of the will and serves to carry on the purely vegetative processes, such as vascular tone, the action of smooth muscle fibers and the regulation of glandular secretion. It therefore enters largely into the emotional states . . ." Essentially the autonomic nervous system may serve as an outlet for energy which is not released in words, thoughts or action because of conflict and repression. The impulses thus conveyed to the nasal structures give rise to a disturbance in function.

Wolff *et al.*[11] do not describe the nature of the conflict or conflicts which they activate. It would be important to determine whether or not there is a specific conflict which gives rise to the changes they observed. Studies[9] have made it clear that a particular conflict expressing itself via the vagus nerve plays an important part in the etiology of peptic ulcer. Might not this be so, also, in certain cases of vasomotor rhinitis?

While the first two patterns involve the autonomic nervous system as a pathway, the third is the result of direct suggestion. The experiment of using an artificial rose to induce an "allergic attack" is an old one, and it has been repeated a number of times. During the attack the nasal mucous membrane will become edematous and pale gray. Within a few minutes of the time that the patient sees that the flower is only paper, the symptoms and the congestion subside. Metzger,[5] an allergist, recently performed this experiment with a paper goldenrod in the month of June.

The response to medication in some cases of vasomotor rhinitis also illustrates the effect of direct suggestion.

In the Asthma Research Council's Report of Progress (1938),[1] it was stated that the results of treatment with a placebo (saline solution) were slightly better than those obtained by protein desensitization. Although the series was small (32 and 35 patients), the study called attention to the influence of suggestion.

For many years it has been known that symptoms can be induced, reproduced and removed by direct suggestion. Charcot demonstrated this fact with the aid of hypnosis. An "allergic attack" precipitated by an artificial flower is such a symptom.

Among the factors which play an etiological role in vasomotor rhinitis are emotional, endocrine, allergic, thermal and constitutional. In certain instances one component predominates while in other cases it is another. Only rough measurements are possible since the nasal dysfunction involves a complex interrelationship of a number of known and perhaps several unknown factors.

Explanations for the interaction of all the various etiological forces have not been worked out, but two theories have been advanced by Urbach[10] to explain the connection between the psychogenic and allergic components. "Perhaps the best explanation is that such influences (emotional) bring an alteration in the excitability of the autonomic nervous system and that stimuli until then of the sub-threshold level thus acquire the capacity of acting as excitants. Another possibility is that psychic stimuli, by their effect on the vascular innervation, bring about a change in the blood supply of the peripheral tissue. The result is that pathologic substances that normally cannot penetrate the vessel walls are now absorbed, leading to an antigen-antibody reaction."

The influence of endocrine changes has received some attention. There are clinicians who believe that a thyroid deficiency is important. According to Proetz,[5] "circulatory changes evidenced chiefly by pallor are to be found in the nasal mucosa in the presence of thyroid insufficiency." Mohun[6] reports that hyperemia and edema of the nasal mucous membrane may develop late in pregnancy in patients who never had symptoms before and that the disturbance is often aggravated in those who had previous trouble. He maintains that there is a definite tendency toward hyperemia and edema when the estrogen level is high. One would suspect that a combination of endocrine and emotional factors operate during pregnancy and that the emotional factors center around conflictual feelings about pregnancy and motherhood.

Although infections may play an etiological role in vasomotor rhinitis, it is probably more common for them to appear as complications. The nasal dysfunction opens the road to bacterial invasion. Fabricant[2] has found that in susceptible persons emotional states "can produce transient conversions of nasal secretions from a normal, slightly acid to an abnormal alkaline state." There is evidence that acidity is unfavorable to the growth of pathogenic bacteria, while alkalinity favors their growth. A shift in the pH of the nose to the alkaline side accompanying vasomotor changes is no doubt one in a group of factors responsible for bacterial invasion.

Sinusitis occurs secondarily and is the result of changes within the sinus lining membrane, direct extension of infection and interference with normal drainage. Other complications may be otitis media and laryngitis. There are emotional sequelae as well. Anorexia, weight loss, insomnia and impairment of efficiency may accompany a prolonged attack. The fatigue in turn aggravates the initial process.

If there are recurrent and prolonged attacks of vasomotor rhinitis irreversible morphological changes are to be anticipated. There will be hyperplasia and later hypertrophy of the surface epithelium. In certain areas the cilia will disappear. The ducts and acini of the mucus glands in the subepithelial layer will be filled with and dilated by secretions. Degeneration into cysts will occur. As the lesion progresses, atrophic changes will be seen and the mucus glands may disappear.

From this discussion it is evident that vasomotor rhinitis is a dynamic process. The picture presented at any particular moment depends upon the interaction of a number of forces and the intensity and duration of the physio-pathological changes. As in any process in motion there will be shifts in the weight of the various etiological factors from time to time. Initially the sensitivity to an inhalant may occupy the center of the stage. Later emotional conflicts may express themselves through this "ready-made" avenue. Innumerable combinations are possible.

It is important to consider vasomotor rhinitis in terms of the total organism. A description of the physiological or pathological state is not enough. Attempts should be made to understand the process on the basis of the various etiological factors that play a part. Emotional influences should not be neglected. Three primary modes of operation have been considered in this article. These mechanisms are not mutually exclusive. They must be viewed in terms of their relationship to one another and in terms of their interaction with other causative agents.

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BOOK REVIEWS AND NOTICES

THE MECHANISM OF ABDOMINAL PAIN. By V. J. KINSELLA, M.B., Ch.M. (Syd.), F.R.C.S. (Eng.), F.R.A.C.S. Pp. 230; 17 figs; 8 plates. Sydney, Australia: Angus & Robertson. Price 32/6.

THE significance of pain of abdominal origin has long been recognized. The interpretation of such pain, however, has been rendered difficult by the conflicting concepts of the mechanisms involved.

The author has given consideration to those accepted concepts of the past, which in general deny the existence of true and direct visceral pain. The erroneous conclusions reached in the past with respect to the existence or non-existence of true visceral pain are due, in the opinion of the author, to the inherent difficulties attendant upon animal experiments in this field. By experiment and observation on human subjects under local anesthesia the author has convincingly demonstrated the sensitivity of diseased viscera without implication of the mesentery and parietal peritoneum. He admits that the mesentery and parietal peritoneum are highly sensitive and frequently contribute to the severity of the abdominal pain of visceral origin, but believes that these structures need not be stimulated to evoke a painful sensation from diseased viscera.

The author further believes that the effective stimulus for pain, both somatic and visceral, is increased tension within the tissues, be that the result of inflammation or muscular contraction.

The concentration of nervous elements within the viscus is low, while the concentration of such elements is relatively high in the mesentery especially along the vessels. The mesenteric border of any given viscus is, therefore, more sensitive than the antimesenteric side. If 1 sq. cm. of mesentery should be crushed, the number of painful stimuli elicited is considerably higher than if 1 sq. cm. of the viscus itself is crushed. Thus, it is that mesenteric pain is said to be of a high order while that of the viscus is relatively low. A narrow segment of bowel may be crushed with a clamp without eliciting a painful response, but if a wider segment is similarly crushed painful stimuli are elicited.

Some attention is directed to the pain associated with some of the commoner clinical disorders, and an attempt is made to explain this upon the basis of pure visceral sensitivity.

The book should prove of special interest to the surgeon. I. R.

INTRACRANIAL TUMORS. By PERCIVAL BAILEY, Prof. of Neurology and Neurologic Surgery, Univ. of Illinois. 2d ed. Pp. 478; 16 plates; 155 figs. Springfield, Ill.: Charles C Thomas, 1948. Price, $10.50.

THIS book combines to an excellent degree neuropathology, neurology and neurosurgery. Both student and the senior neurosurgeon will be well advised to consult it. The parts on neuropathology, as is to be expected from this author, cover all demands. The illustrations are adequate, the pen and ink drawings of the microscopic fields showing cell detail surprisingly well. The drawings of the gross specimens of tumors *in situ* are less effective. The weakest section deals with the surgery of brain tumors. Constant reference is made to methods formerly used in the Brigham Hospital and there have been neurosurgical advances since 1930, few of which are recorded. But, as the author states in his preface, this book has been written for students who need not be too greatly interested in operative detail. If they take up neurosurgery and find themselves in a modern clinic, their conception of neurosurgical technique can be properly learned by first-hand experience.

F. G.

ROENTGEN STUDIES OF THE LUNGS AND HEART. By NILS WESTERMARK, M.D., Caroline Institute, University of Stockholm, Sweden. Pp. 216; 98 ills. Minneapolis: Univ. of Minnesota Press, 1948. Price, $7.00.

THIS excellent monograph contains a series of guest lectures given by an eminent Swedish radiologist at Minneapolis. The approach is primarily through application of principles of physiology and the alterations in them occurring in disease. This point of view is indicative of the new attitude toward roentgen investigations as a whole but particularly as it is directed toward the chest. The stimulating observations are profusely illustrated and documented and represent a very rich experience during 20 years' practice in a teaching institution. Perhaps the most interesting and provocative chapters deal with the importance of the intra-alveolar pressure in the diagnosis of pulmonary diseases and the roentgen diagnosis of pulmonary embolism.

The American physician may encounter some difficulty in accepting some of Dr. Westermark's statements in regard to pulmonary

physiology and it must be admitted that a few of the important points which are made in the text cannot be easily seen on the illustrations. In spite of the unfamiliar method of thinking which the reader may encounter, or possibly because of it, this little book will make a graceful addition to the library of all who are interested in the chest, its function and diseases. R. B.

MEDICAL HYPNOSIS. By LEWIS R. WOLBERG, M.D., Asst. Clinical Prof. of Psychiatry, New York Medical College. 2 vols. Pp. 439 and 513. New York: Grune & Stratton, 1948. Price, $5.50 and $6.50.

THIS is a comprehensive work by a man well qualified to write on the subject. Psychoanalytically trained, he was taught the technique of induction of hypnosis by Dr. M. H. Erickson.

A summary of the contents is presented in the preface: "A considerable portion of Volume I is devoted to a step-by-step description of the induction process, illustrating various induction methods by excerpts from transcriptions of actual hypnotic sessions. There is a didactic discussion of the principles of psychotherapy, and of the psychopathologic factors in the different disease syndromes. Therapeutic methods . . . are elaborated on in some detail. . . . Volume II contains 3 complete transcribed case histories which enable the reader to . . . observe the therapeutic management of the patient . . . as these illustrate a preceding discussion of the uses and limitations of the chief short-term psychotherapeutic methods."

The 2 volumes contain a wealth of information which will be of interest to everyone who is concerned with psychotherapy in general and with the employment of hypnosis in particular. The detailed recordings of case histories are especially worth noting. Numerous references to the literature on hypnosis are included. W. P.

VASCULAR DISEASES IN CLINICAL PRACTICE. By IRVING SHEKWOOD WRIGHT, M.D., Assoc. Prof. of Clinical Medicine, Cornell Univ. Medical College. Pp. 514; 104 ills. Chicago: Year Book Publishers, 1948. Price, $7.50.

THIS work presents the clinical aspects of diseases of the arteries, veins and lymphatics in a clear and concise manner. About half the book is devoted to diseases of the arteries, one-seventh to the veins and the rest to miscellaneous vascular conditions. The chapter on Methods of Study of the Patient is particularly well done. The chapter on the Hyperabduction Syndrome, based on the author's work, is instructive. The author's opinion concerning the merits of various forms of therapy is particularly valuable, in view of his large clinical experience.

The book is a valuable addition to the literature on vascular diseases, not only to the practitioner and internist, but also to those who make these diseases their major interest. M. N.

BACTERIAL AND VIRUS DISEASES. By H. J. PARISH, M.D., Clinical Research Director, Wellcome Foundation. Pp. 168; 14 ills. Balt.: Williams & Wilkins, 1948. Price, $2.75.

AS THE subtitle (Antisera, Toxocils, Vaccines and Tuberculins in Prophylaxis and Treatment) indicates, this useful little handbook deals with the theoretical concepts of immunity, methods of preparation and standardization of therapeutic antisera and biologic preparations, methods of diagnosing susceptibility, and specific instructions as to serologic treatment of bacterial and viral diseases. At the end of the volume is a short historical sketch of developments in this field. As the author indicates in the preface, the book is designed to aid the busy practitioner in a better understanding of the principles underlying the prevention and treatment of infectious diseases. For American practitioners, however, it should be pointed out that dosages and the standardization of biologic preparations are based upon current British usage, which differs in some cases from those employed in the United States. R. N.

RACIAL VARIATIONS IN IMMUNITY TO SYPHILIS. By CHESTER NORTH FRAZIER, M.D., SR.P.H., and LI HUNG-CHIUNG, M.D. Pp. 122. Chicago: University of Chicago Press, 1948. Price, $2.50.

THIS monograph is the first comprehensive and scientific presentation of the actual differences in the reaction to syphilitic infection among Chinese, Europeans and Americans. The authors have demonstrated the patterns of syphilis by the elective localization in tissues and organs of Chinese population as compared with American White and Negro races, a reasonable comparison from the medical, geographic and other viewpoints. In the people of the 3 races they have analyzed 16,845 consecutive cases of syphilis, extending over a period of 10 years, July 1, 1927, to June 30, 1937. They found that "regardless of race or sex, the disease was essentially the

same in all people. Differences between races lay almost entirely in the relation frequency with which the phenomena of the disease developed. People of all three races had lesions of the skin and bones, of the brain and spinal cord, and of the heart and blood vessels." In spite of this similarity of pattern of syphilis in the 3 races, the authors found that in several important respects the disease was a less serious matter in the Chinese than in either the Whites or Negroes. The basis and probable mechanisms of this concept are outlined in detail.

Written by two competent authorities, this volume is interesting, well-composed, and attractively presented. The results will go a long way in helping to differentiate the effects of *Treponema pallidum* on an organism from the influence of moral and other factors which may be responsible for the so-called "immunity" enjoyed by certain races.

In the treatment of the literature, it would have been worth while to mention the efforts of other workers who have attempted better definition of the manifestations of syphilis as they occur in the American Negro at least, particularly Hazen. Otherwise, this is a praiseworthy handling of an important problem of syphilology. H. B.

CLINICAL OPHTHALMOLOGY. By H. M. TRAQUAIR, M.D., Consulting Ophthalmic Surgeon, Royal Infirmary, Edinburgh. Pp. 264; 72 ills., 8 in color. St. Louis: C. V. Mosby, 1948. Price, $9.00.

THE author states in his preface that the book might be called "Ophthalmology without an ophthalmoscope." The omission of examination of the fundus with the ophthalmoscope the reviewer feels is a mistake. In the teaching of medicine in the medical schools of the United States, the student is becoming instructed more and more in the use of the ophthalmoscope. There is no reason why a general practitioner should not be able to make an examination of the fundus adequate to detect gross changes, such as hemorrhages and exudates and the general condition of the retinal blood vessels. If the use of the instrument is begun early, the physician will become sufficiently adept with it to enable him to tell whether or not the fundus is normal, and if not to refer the patient to someone who is more expert.

Apart from this defect, the book is excellent. The external diseases are well described and illustrated and there is much of practical value to be found. It can be recommended to every general physician as a working text for all ophthalmic conditions except those relating to the fundus oculi. F. A.

SURGICAL TREATMENT OF THE ABDOMEN. Edited by FREDERIC W. BANCROFT, M.D., F.A.C.S., Prof. of Clinical Surgery, New York Medical College, and PRESTON A. WADE, M.D., F.A.C.S. Pp. 1026; 457 ills.; 3 color plates. Phila.: J. B. Lippincott, 1947. Price, $18.00.

THIS is an enlarged, completely revised edition of an earlier work published by Appleton-Century under the title of "Operative Surgery". Thirty-six eminent contributors have provided excellent discussions of the surgical treatment of disorders of the alimentary tract, biliary tract, liver, pancreas, and spleen. In addition to surgical techniques, and pre- and postoperative care, there are included sections on blood transfusions, anesthesia and fundamental principles of surgical technique. No attempt is made to discuss symptomatology or differential diagnosis. The up to date and authoritative discussions deal with treatment or treatments of a given lesion. This book should be available to all who are interested in abdominal surgery. H. Z.

RECENT PROGRESS IN HORMONE RESEARCH. Edited by GREGORY PINCUS. Proceedings of the Laurentian Hormone Conference. Vol. II. Pp. 427; illustrated. New York: Academic Press, 1948. Price, $8.00.

THESE papers, dealing with highly specialized aspects of endocrinology by those who are doing research in the field, are grouped under 5 headings: 1. physical methods in hormone research; 2. pituitary control and activity; 3. hormone metabolism; 4. hormonal regulation of metabolism; 5. aspects of clinical endocrinology.

Many charts and figures illustrate the data presented and most of the papers are presented in an admirable manner. Following each paper there is reported the informal discussion of those participating in the conference and this adds a great deal to the interest of the volume. Use of the data is facilitated by an index.

In the matter dealing with clinical aspects, the Reviewer deplores the procedure of determining human sperm counts, accomplished by methods which moralists condemn as immoral misuse of the sexual function. In the discussions of the administration of male sex hormones to patients there seems to be a concentration of interest on the physical effects resulting, without advice of avoiding overstimulation with its associated psychological effects. I. Z.

NEW BOOKS

Conference on Liver Injury. Transactions of the Fifth Meeting. Pp. 127; 30 ills. *Liver Injury.* Transactions of the Sixth Conference. Pp. 74; 9 ills. New York: Josiah Macy, Jr., Foundation, Sept. 26-27, 1946; May 1-2, 1947. Price, $2.25 and $2.00.

For some years past the Josiah Macy, Jr., Foundation has sponsored conferences on liver injury. The conferences are round-table discussions of subjects of interest to clinicians and investigators of liver injury in the broadest sense. The 5th and 6th Conferences deal with such important subjects as the relation of dietary factors to chemical injury, impairment from vitamin deficiency, liver function studies, chronic hepatitis, therapy in liver diseases, cirrhosis, the hepatorenal syndrome, chromatography in the study of liver diseases, and massive hepatic necrosis. Each subject is briefly presented and the resulting discussion summarized.

The Conferences on Liver Injury are valuable, and afford an excellent survey of present day investigations in the liver field.

B. L.

Agonal Acidosis. By Ib Fabricius-Hansen, Oresunds Hospital. Translated by Hans Andersen, M.M. Pp. 134. Copenhagen: Povl Branner; New York: Stechert-Hafner, 1948. Price not given.

This monograph is a report of a detailed study just antecedent to death of the acid-base and electrolyte balance in a series of cases. The monograph contains discussion and experimental data of interest to the specialist in this field.

W. S.

Handbook of Ophthalmology. By Everett L. Goar, M.D., Prof. of Opthalmology, Baylor Univ. College of Medicine. Pp. 166; 48 ills, 7 color plates. St. Louis: C. V. Mosby, 1948. Price, $5.50.

This book is the outcome of a series of lectures delivered to medical students. The author has made an attempt to condense the knowledge a medical student and a general practitioner should have of ophthalmology. The selection of the material he has made will be criticized or applauded, depending upon what the reader thinks is important. Obviously there will be no unanimity of opinion. The book will probably serve its purpose as an introduction to ophthalmology, but can hardly be regarded as a serious text for the general practitioner. It can be recommended only as a primer.

F. A.

The Psychological Origin and Treatment of Enuresis. By Stevenson Smith, Ph.D. Pp. 70. Seattle: University of Washington Press, 1948. Price, $1.75.

This little book offers a concise discussion of the psychology of enuresis. The material is "down to earth" yet on the whole the ideas expressed are acceptable to even advanced students of child behavior. It should constitute a valuable aid to physicians and parents who cope with the problem of bed-wetting. It is concise, humorous and very helpful.

V. H.

20th Century Speech and Voice Correction. Edited by Emil Froeschels, M.D. 19 contributors. Pp. 321; 33 ills. New York: Philosophical Library, 1948. Price, $6.00.

Though differing occasionally, these contributors have given us a helpful book. Of the 22 chapters, Dyslalia is accorded most space; this includes all functional defects of articulation, common causes being deafness, inactivity of muscles of articulation, mental deficiency, hyperemotionality, and injuries to various oral parts. Prosthetic Therapy of the Cleft Palate is a well illustrated chapter.

N. Y.

Medical Clinics of North America. Symposium on Psychiatry and Neurology. New York Number. Pp. 558-853. Phila.: W. B. Saunders, May, 1948. Price, $16 a year.

The editor points out that the material covers a wide field in the ever expanding domain of psychiatry and neurology. Many of the articles are probably much too technical for those outside the specialty. If this "Symposium" is for the benefit of the general practitioner it would seem that a much more satisfactory choice of articles could have been made.

Among the most valuable papers are: Headache, An Outline for Diagnosis and Treatment; Anxiety States, Their Recognition and Management; Differential Diagnosis of Coma. On the other hand there are those that are either exceedingly technical (*i. e.*, "Hypnotic Psychotherapy"), or else founded upon principles which are controversial (*e. g.*, "Electroshock Therapy in an Out-patient Setting"). Some of the psychodynamics put forward are open to question (*e. g.*, "Alcoholism, Its Nature and Treatment"). Any symposium of this type for the general practitioner should contain only material which is generally accepted by the specialists in the field and should avoid articles of too technical nature.

D. A.

NEW EDITIONS

A Textbook of Gynecology. By Emil Novak, M.D., F.A.C.S., Ass't Prof. of Gynecology, Johns Hopkins Medical School. 3d ed. Pp. 742; 484 ills. Balt.: Williams & Wilkins, 1948. Price, $8.00.

In this edition, the author has just about covered the non-operative portion of gynecology. In the discussion of sterility no mention is made of the work by Farris upon the timing of ovulation. Only one page is devoted to the subject of the anatomy of the pelvic floor.

The book is written through the eyes of a combined clinician, endocrinologist and pathologist and every page reflects the importance of each of these fields in the teaching and the practice of modern gynecology. The writing is so facile that the reading is effortless. Many of the illustrations are in color and both the microscopic and the gross pictures are purposeful and lucid. The chapters upon functional gynecological disturbances and upon bachache are especially replete with valuable information and sound advice.

As one reviews the book as a whole, the impression arises that it will be more readily assimilated by and therefore more valuable to the general practitioner and the younger specialist than to the undergraduate student.

F. P.

Laboratory Diagnosis of Protozoan Diseases. By Charles Franklin Craig, M.D., Emeritus Prof. of Tropical Medicine, Tulane Univ. Medical School. 2d ed. Pp. 384; 56 ills., 7 color plates. Phila.: Lea & Febiger, 1948. Price, $6.50.

The new edition of this book has been enlarged by 35 pages. Plates in color of the plasmodia of malaria and a number of newer diagnostic methods have been added. It would have been improved further had the author dropped some of the out-moded methods and been more critical of those which are included and more explicit in his statements of their value and the conditions under which they may be used. H. R.

Diseases of the Chest. By Robert Coope, M.D., B.Sc., F.R.C.P., Hon. Physician, Royal Liverpool United Hospital. 2d ed. Pp. 541; 168 ills., 8 in color. Edinburgh and Balt.: Williams & Wilkins, 1948. Price, $7.50.

This book is designed for "students and practitioners". The first 6 chapters are devoted to the physiological and anatomical principles underlying diseases of the lung, with emphasis upon the segmental divisions of the lung lobes, and to the fundamental principles of physical diagnosis.

The main portion of the text is devoted to descriptions of the various acute and chronic lung diseases. The more common conditions are covered fairly completely; the rarer conditions receive at least a few paragraphs, to aid in tre differential diagnosis. Diseases of the pleura and mediastinum are also covered, and there are chapters on chest injuries, oxygen therapy, and disturbances of the pulmonary circulation. The use of sulfonamides in pulmonary infections is discussed, but little space is given to penicillin, and streptomycin is not mentioned; this is undoubtedly due to the scarcity of those drugs in Great Britain.

The book is very well written, and contains numerous drawings to illustrate important points of the text. There is only one plate—an x-ray of a normal chest—in the main portion of the book; an appendix contains reproductions of 32 illustrative films.

This is not a reference book on pulmonary diseases, but can be recommended for general use to students and general practitioners.

H. H.

A Handbook for Dissectors. By J. C. Boileau Grant, Prof. and Director, and H. A. Gates, Prof. of Anatomy, Univ. of Toronto. 3d ed. Pp. 415; 19 figs. Balt.: Williams & Wilkins, 1948. Price, $3.00

This is a dissecting guide for use in conjunction with a *Method of Anatomy*, the textbook by Dr. Grant. It is in no sense a textbook of anatomy and can not be used alone. Its value is limited mainly to the beginning student in the dissecting laboratory. W. W.

Midwifery. By Ten Teachers, Directed by Clifford White, M.D., F.R.C.S. (Eng.). 8th ed. Pp. 560; 217 figs. Balt.: Williams & Wilkins, 1948. Price, $6.00.

Essentials of College Chemistry. By C. H. Whiteford, Ph.D., and R. G. Coffin, M.S. 3d ed. Pp. 632; 76 figs. St. Louis, C. V. Mosby, 1948. Price, $4.75.

Recent Advances in Obstetrics and Gynecology. By Aleck W. Bourne, M.A., M.B., F.R.C.S. (Eng.), and Leslie H. Williams, M.D., M.S., F.R.C.S. (Eng.). 7th ed. Pp. 326; 85 ills. Phila.: Blakiston, 1948. Price, $6.00.

Clinical Laboratory Methods and Diagnosis. By R. B. H. Gradwohl, M.D., D.Sc., F.R.S.T.M. & H. (London). 3 Vols. 4th ed. Pp. 3300; 1100 ills., 56 color plates. St. Louis: C. V. Mosby, 1948. Price, $40.00.

Outline of Physiology. By William R. Amberson, Ph.D., and Dietrich C. Smith, Ph. D. 2d ed. Pp. 502; 192 figs. Balt.: Williams & Wilkins, 1948. Price, $5.00.